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REVIEW® of Ophthalmology

March 2017

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ANNUAL CATARACT ISSUE

NEW APPROACHES COME INTO FOCUS

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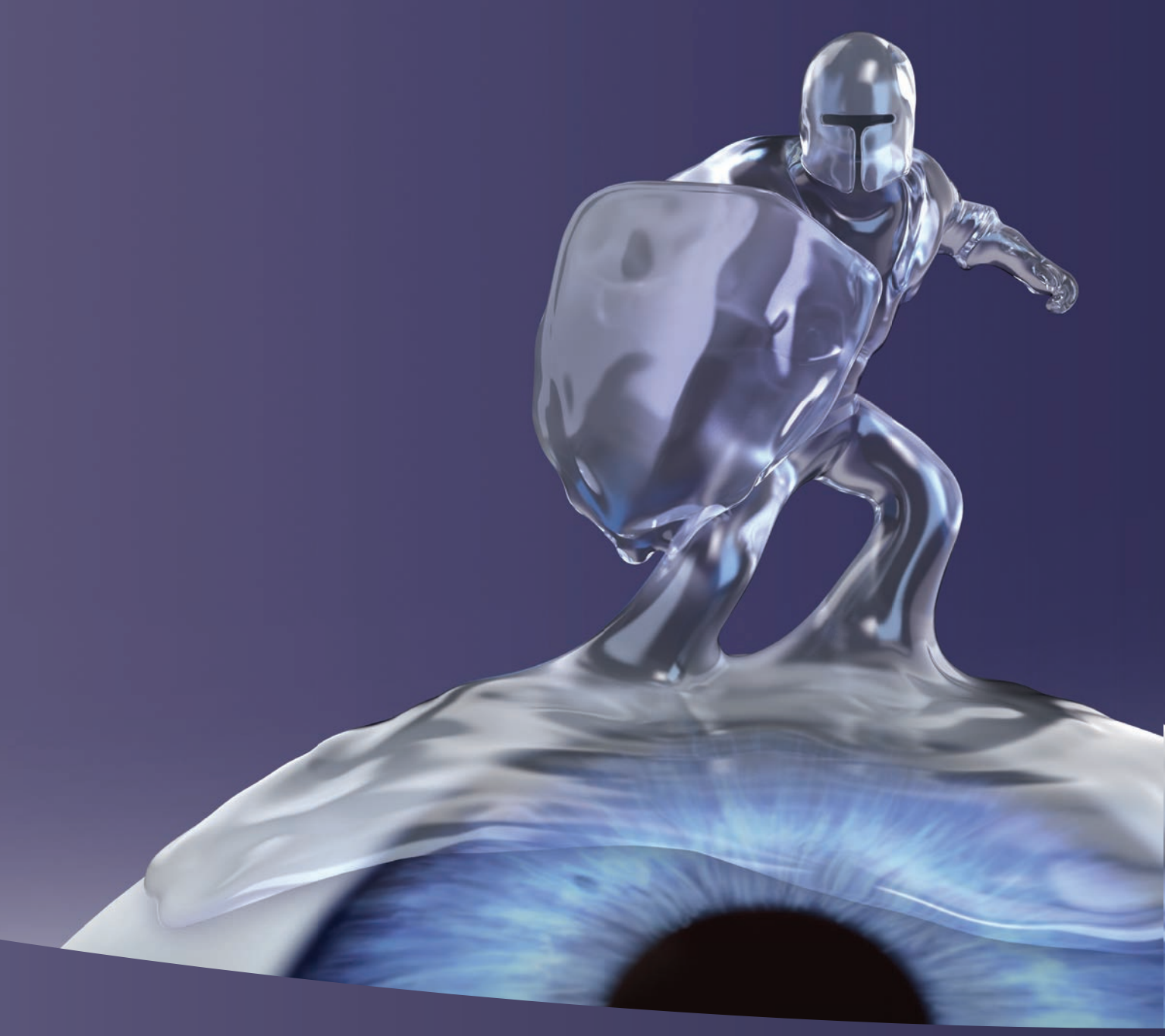

Indications and Usage
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

  It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular

A DROP OF PREVENTION

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- Ensures complete coverage throughout the day with BID dosing[1]

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Formulated with DURASITE® DELIVERY SYSTEM

surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

- BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.
- The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see brief summary of full Prescribing Information on the adjacent page.

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139. **4.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed July 18, 2016. **5.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66.

SUN OPHTHALMICS

BromSite™ (bromfenac ophthalmic solution) 0.075% Brief Summary

INDICATIONS AND USAGE
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of BromSite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Use with Other Topical Ophthalmic Medications
BromSite should be administered at least 5 minutes after instillation of other topical medications.

Dosage Forms and Strengths
Topical ophthalmic solution: bromfenac 0.075%.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy

Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite during late pregnancy should be avoided.

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, advise patients to administer BromSite at least 5 minutes after instillation of other topical medications.

Concomitant Use of Contact Lenses
Advise patients not to wear contact lenses during administration of BromSite. The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses.

Sterility of Dropper Tip/Product Use
Advise patients to replace the bottle cap after use and do not touch the dropper tip to any surface as this may contaminate the contents.

Advise patients to thoroughly wash hands prior to using BromSite.

Rx Only
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SUN OPHTHALMICS

REVIEW NEWS
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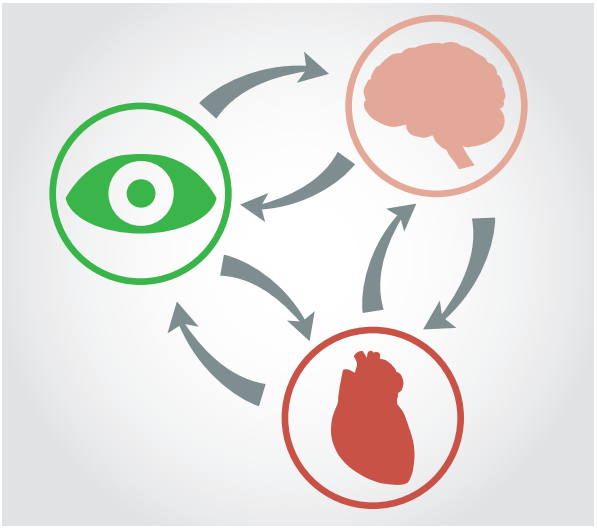
When LDL Goes Down, Do Cataracts Go Up?

Researchers in a study recently published in the *Journal of the American College of Cardiology* aimed at evaluating the safety of the cholesterol-lowering drug alirocumab were relieved to find the drug didn't induce an unusual number of neurological or neurocognitive events, but were surprised to discover that a very low low-density lipoprotein level might result in cataract formation.

Alirocumab is a member of a new class of monoclonal antibody drugs called proprotein convertase subtilisin/kexin type 9 inhibitors, or PCSK9 inhibitors. They're designed for patients with high cholesterol that's uncontrolled by conventional statin therapy or who can't tolerate a statin. Some of these patients have hereditary conditions that cause extremely high cholesterol. When added to a statin in these patients, a PCSK9 inhibitor can lower a patient's cholesterol by as much as 60 percent.[1]

In the study, researchers pooled the data from 14 trials (double-blind treatment for eight to 14 weeks; n: 3,340 alirocumab; 1,894 controls [placebo or the cholesterol drug ezetimibe]). They found similar rates of adverse events in patients with an LDL less than 25 and those with LDL less than 15. However, in a propensity score analysis, patients with LDL less than 25 had a higher rate of cataracts (2.6 percent) than those with a cholesterol score of 25 or greater (0.8 percent; hazard ratio: 3.4; 95 percent confidence interval: 1.58 to 7.35).[2]

Lead author Jennifer Robinson, MD, MPH, is a professor in the epidemiology department at the University of Iowa College of Public Health and director of the college's Preventive Intervention Center. She says the cataract results are puzzling. "It was reassuring that, in one sense, the PCSK9 inhibitor didn't have an effect on other bodily functions, but we did note that those patients with very low LDL did have a higher rate of cataracts or cataract surgery," she says. "We don't know if it was caused by the PCSK9 drug or because the people that ended up with very low LDL levels on the PCSK9 inhibitor started with lower LDL levels, had diabetes, were older, had cardiovascular disease, were male or had some other risk factor for cataracts. What it does tell us is that it's a potential side effect. We looked at other studies, and noted cataract in one statin study where the patients got low LDLs, but we didn't find it in a different study in which patients also had low LDL after treatment. So, we really don't know."



In the study, Dr. Robinson and her co-authors postulate some possible mechanisms behind the finding. They note that cholesterol that's needed by the crystalline lens is synthesized *in situ* and that, in animal toxicity studies, high doses of statins have been shown to inhibit lens cholesterol biosynthesis and promote cataract formation, but this result hasn't been reproduced in human studies.[2] They go on to say that studies have shown an increased rate of cataract after statin treatment, and that cataract has also been assocated with hyperglycemia and blood pressure levels. "It could be that acute LDL-C lowering accelerates underlying aging or metabolic syndrome or diabetes-related changes, contributing to cataracts," they write.[2]

Dr. Robinson says an upcoming study may shed more light on the situation. "The FOURIER study, a large study of 27,000 patients who are on cholesterol medications, is due to be released in March 2017 at the American College of Cardiology," she says. "That study will give us a good handle on whether or not there's any safety signal for cataracts in patients who get

to a very low LDL level. At this point, we actually don't think the cataract finding is due to the drug itself, because when we looked at the data, in the whole PCSK9 program there was no cataract signal. It could be due to the low cholesterol levels themselves."

She adds that, in the long run, even if cataract winds up being a proven side effect of these drugs, physicians and patients may need to weigh the risks vs. the benefits of the new therapies. "The reason we're lowering bad cholesterol is to prevent heart attacks and strokes," she says. "So, at the end of the day, you have to weigh that with the adverse events. If we find a dramatic reduction in heart attack and stroke in these large trials, we have to take that into consideration. Not to minimize cataracts, but in the grand scheme of things, they aren't as bad as dying from a stroke."

There's also the question of the study's adverse event findings' clinical relevance in the real world, in light of the kinds of patients who will be taking these drugs. "One group of patients who will be candidates are those with genetic high cholesterol, and having a low LDL isn't the problem with them because they're starting at levels of 300 or 400," Dr. Robinson says. "Where it will be an issue is if, on the basis of these ongoing trials, we find that people with heart disease benefit from these drugs. In that case, we're probably going to have to be a little more careful about who we select to receive them, because they're quite expensive—around $15,000 per year. They're not for everyone, though the very high-risk people whose cholesterol is high on a statin would probably be reasonable candidates. If that's the case, then, getting low LDLs isn't a consideration anymore, so cataract may not be a clinical issue for these patients."

Another possible finding might be that, similar to patients who take statins and wind up getting diabetes, these new cholesterol-lowering drugs may just be speeding up the inevitable. "A lot of people who develop diabetes while on a statin would be at risk for diabetes anyway even if they weren't on a statin," Dr. Robinson says. "As it happens, there's a small excess risk for diabetes in statin-treated patients vs. people who don't get statins. It turns out that all we do is nudge them into diabetes a couple of months earlier because they had diabetes risk factors and were going to get it anyway. So, in the case of cataract and low LDL levels and/or PCSK9 inhibitors, these factors may be tipping people a little earlier into cataract who would have developed cataracts anyway. That's speculation, and we don't have data to support that, but I don't think we're causing cataracts in totally normal lenses."

1. Seidah NG. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors in the treatment of hypercholesterolemia and other pathologies. Curr Pharm Des 2013;19:17:3161-72.
2. Robinson JG, Rosenson RS, Farnier M, et al. Safety of very low low-density lipoprotein cholesterol levels with alirocumab: Pooled data from randomized trials. J Amer Coll Cardiol 2017;69:5:471-482.

The Hazards of Detergent Pods to Children

With the widespread use of detergent pods, more and more children are admitted to the emergency room with ocular burns. In the span of three years, the instances of admission spiked from just 12 reported cases to 1,201.[1] In hopes of understanding this spike in ocular burns in children, researchers at the Johns Hopkins Center for Injury Research and Policy released a study documenting the supposed causes of these injuries.

Researchers consulted the National Electronic Injury Surveillance System, focusing specifically on children aged 3 to 4 years (i.e., preschool-aged children) reasoning that children younger than 3 wouldn't usually be strong enough to damage a detergent pod. They used the NEISS to search for narrative summaries that referenced the laundry detergent pods, looking specifically at the year, sex, race/ethnicity, setting and the circumstances leading to the injuries.

Based on data from the NEISS, between January 1, 2010 and December 31, 2015, 1,201 laundry detergent pod-related ocular burns occurred among children ages 3 to 4. The proportion of all chemical ocular injuries associated with these devices increased from 0.8 percent of burns in 2012 to 26 percent in 2015.[1] All patients were treated and released from the emergency department. Patients were mostly white (46.3 percent) and non-Hispanic (88.7 percent).[1]

Sterling Haring, DO, MPH, the author of the study, comments on the cause of this spike in ocular burns. "I think it's really two things," he says. "First we're seeing increased market penetration of the pods. They're cheaper, so people are buying them and keeping them in their home more. They're more common. Number two, I think, is that they have been in homes longer. Within the first month that a person goes out and buys these, they probably keep their kids away from them because they aren't as comfortable with them. As people handle and use them more, they get more comfortable with them and don't see them the same way they would bleach."

Dr. Haring, however, provides some preventative advice to hopefully reverse the increasing instances of burns. "There have been a lot of reports on different types of poisoning associated with these things, so it's pretty clear they're not the safest of objects, but if you're going to have them in your house, keep them up, away and out of sight. That's the best advice. Anyone with kids knows that if kids see it, they can get to it," he says. "Number two is, if you see your kid playing with one, take it away. It may look safe, but it's

not. Obviously the key point here is to make sure you wash your child's eyes if they exposed themselves to these pods, and don't hesitate to call 911."

1. Haring S, Sheffield I, Frattaroli S. Detergent pod-related eye injuries among preschool-aged children. JAMA Ophthalmol; Published online February 2, 2017.

Stanford Awarded Vision Grant

Research to Prevent Blindness recently awarded Stanford University's Department of Ophthalmology a four-year, $300,000 grant to promote cutting-edge ophthalmology and vision science research.

In a statement issued by the University, Jeffrey Goldberg, MD, PhD, professor and chair of ophthalmology, says plans are already under way for making use of the funds. "I couldn't be more pleased to engage the support of RPB and their outstanding scientists and advisers," Dr. Goldberg says. "We are planning to support projects that leverage collaborations between scientists in the Department of Ophthalmology and across the breadth of Stanford's campus."

Potential projects in the works include an investigation of brain stimulation to boost vision in patients with retinal or optic-nerve degeneration, and work to identify molecular pathways to cue a retina to self-repair when damaged by disease, Goldberg says. REVIEW

Correction

From Bausch + Lomb:

In the February 2017 issue of *Review of Ophthalmology*, a claim was presented on the cover tip advertisement for the Trulign toric IOL that stated: "Only one lens brings astigmatism AND presbyopia into focus." In light of recent FDA approvals, justification for this claim can no longer be maintained. Bausch + Lomb Incorporated regrets this oversight and has revised its advertising to reflect the current marketplace.

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IMPORTANT SAFETY INFORMATION

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% must be added to irrigation solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015.

Please see the Full Prescribing Information at www.omidria.com/prescribinginformation.

*Individual insurance coverage and policies may vary, and Omeros does not guarantee insurance coverage or payment. Omeros offers payments under the OMIDRIAssure "We Pay the Difference" program on behalf of qualifying patients. OMIDRIAssure is subject to change without notice.

Visit www.omidria.com

OMEROS

OMIDRIA®
(phenylephrine and ketorolac injection) 1% / 0.3%

Is astigmatism making your patients' butts look big?

There's a good chance it is, since the overwhelming majority of cataract patients suffer from astigmatism. But all joking aside, there's nothing funny about the way it can impact visual outcomes. That's why LENSAR® has released Streamline™ III, the third LENSAR Laser System upgrade in two years. With the latest enhancements, including wireless transfer* of pre-op diagnostics data and Total Corneal Astigmatism, post-op outcomes optimization, iris registration, and IntelliAxis™ steep axis corneal marking, you can confidently and precisely manage astigmatism and deliver the outstanding outcomes your patients will be happy to see.

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* Available with the Cassini® Corneal Shape Analyzer. USB integration available with Nidek® OPD.

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REVIEW® of Ophthalmology

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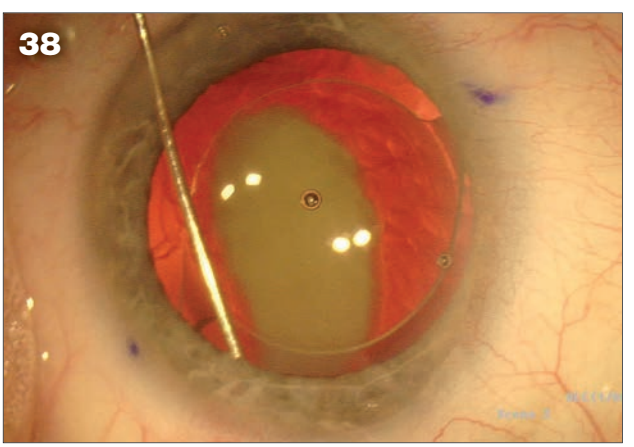

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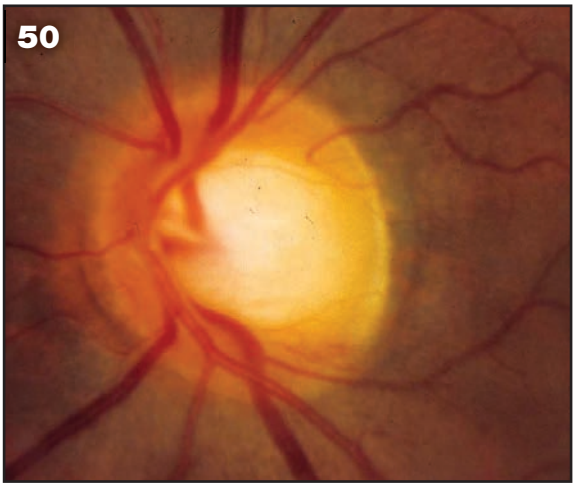

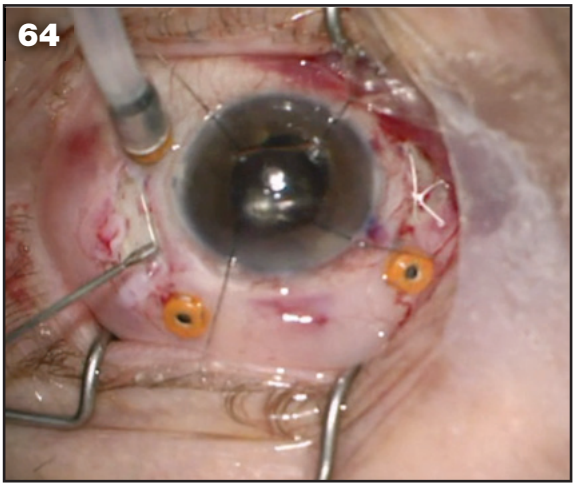

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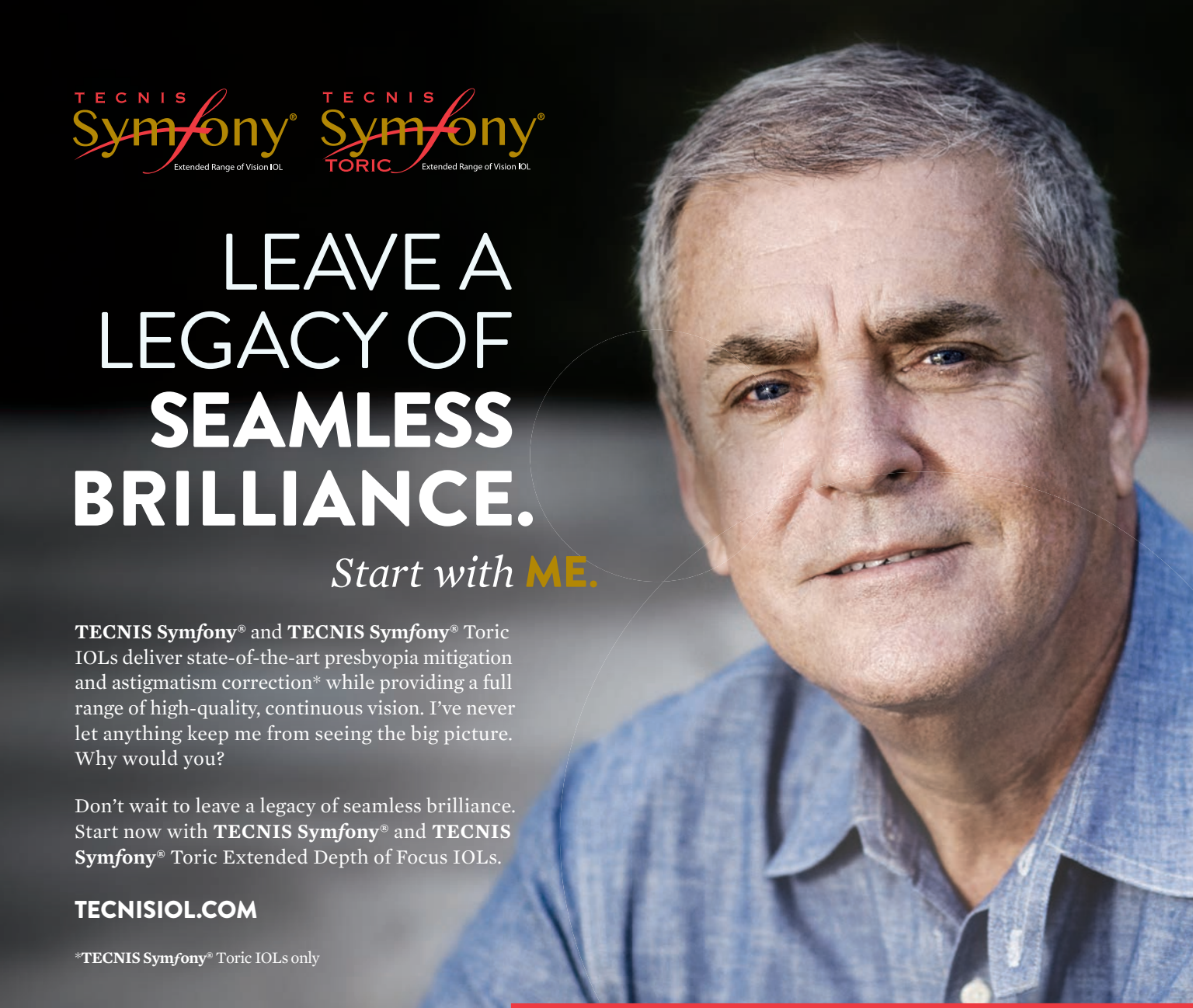

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INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE TECNIS SYMFONY® AND TECNIS SYMFONY® TORIC EXTENDED RANGE OF VISION IOLs

Rx Only

INDICATIONS: The TECNIS Symfony® Extended Range of Vision IOL, model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The model ZXR00 IOL is intended for capsular bag placement only. The TECNIS Symfony® Toric Extended Range of Vision IOLs, models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The model series ZXT IOLs are intended for capsular bag placement only. **WARNINGS:** May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. Rotation of the TECNIS Symfony® Toric IOLs away from their intended axis can reduce their astigmatic correction, and misalignment greater than 30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. **ATTENTION:** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

Abbott

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REVIEW Editor's Page

Walter C. Bethke, Editor in Chief

Efficacy Has No Expiration Date

In his new book, "The Revenge of Analog: Real Things and Why They Matter," author David Sax documents the resurgence of technologies many of us had written off as dead and buried, such as vinyl records (and the stores that sell them), actual books (not just digital versions), and pens and worn notebooks (for capturing ideas and finding inspiration). He cites startling statistics and anecdotes as evidence for this comeback, such as that the number of vinyl records being pressed and sold has increased tenfold since 2006, and that even high-tech visionaries, when they sit down to meet with him, whip out moleskin notebooks—not smartphones—when it comes time to give form to a fleeting concept.

Mr. Sax is quick to point out that this re-emergence isn't an affectation: People, many of them young, are choosing to use these older technologies because they appreciate the concrete benefits they bring. About these users he writes, "They are incredibly forward thinking and innovative, and use every tool at their disposal—online crowdfunding, social media, design software, smartphones—to bring analog goods and services to market. They aren't pushing the digital world away. Rather, they're pulling the analog one closer, and using its every advantage to succeed."

"Using its every advantage to succeed." This sounds like a cataract surgeon eyeing a new device: Whether it's new or old, if it works well, it's going to be used.

Surgeons have always had a critical eye regarding new technology—they're inundated with too many new choices not to. In this month's cataract surgery issue, they take on many of their specialty's newest technologies, and, similar to Mr. Sax's book, in many cases discuss how they stack up against their old methods.

In Christopher Kent's article on outcomes of femtosecond laser-assisted cataract surgery *(p. 22)*—the standard-bearer for ophthalmic high technology—expert surgeons break down this new modality and discuss its pros and cons relative to what they currently do. The questions they ponder are echoed by many of their colleagues.

In pharmaceuticals, too, surgeons are faced with new choices. Though the technology used in dropless and less-drops surgery isn't new, the ideas behind them are, as Senior Associate Editor Kristine Brennan found out while speaking to surgeons about the pros and cons of this emerging approach to postop infection and inflammation prevention *(p. 38)*.

Intraocular lens technology is just as critical to your outcomes as your cataract-removal equipment. With that in mind, Associate Editor Liam Jordan lays out the data from three new toric IOLs, accompanied by advice from the experts who use them, beginning on p. 32.

Here's hoping these articles get you thinking about your technologies, both old and new, and what benefits they offer your practice. (Though you can probably leave the Betamax in the attic.)

— Walter Bethke, Editor in Chief

Discover Strength in efficacy

As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/ro

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Please see brief summary of full Prescribing Information on the following page.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

06/2016
US-LEA-1648(1)

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA.

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

6.3 Postmarketing Experience. The following adverse reactions have been identified during postapproval use of EYLEA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity including rash, pruritus, and urticaria as well as isolated cases of severe anaphylactic/anaphylactoid reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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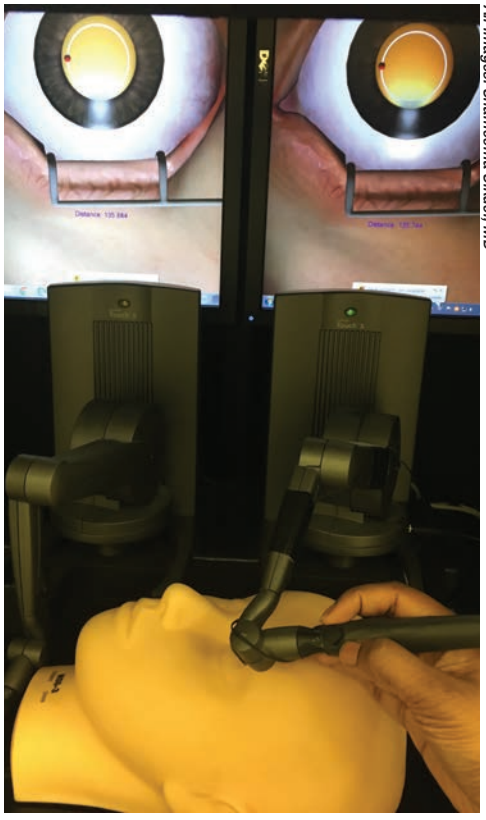
Imitation of Life: Phaco Simulators

Virtual reality simulators are assuming increasing importance in residency training. Here are two on the market today.

Kristine Brennan, Senior Associate Editor

Although cataract procedures are the most commonly performed ophthalmic surgeries, they demand uncommon motor control and concentration. According to a 2002 survey of 129 American ophthalmology training programs, the mean number of cataract procedures residents performed while in training was 113.[1] Since that survey, virtual-reality surgical simulators have begun assuming an important role in phacoemulsification skills training, alongside traditional wet-lab work and master-apprentice training in the OR. Growing legal and ethical concerns surrounding the use of human patients as teaching cases, along with with reported increased costs in terms of experienced surgeon time and complication rates with resident-performed procedures,[2] are prompting interest in alternative surgical training models.

Here is a look at two VR cataract surgery simulators: the venerable Eyesi (VRMagic, Manheim, Germany) and relative newcomer MicroVisTouch (ImmersiveTouch, Chicago).



All images: Shameema Sikder, MD

The MicroVisTouch features a blunt-tip handpiece attached to a robotic arm. The virtual reality platform transforms the handpiece into whichever cataract instrument the trainee needs to perform a given surgical step during a simulated procedure.

MicroVisTouch

Shameema Sikder, MD, director of Johns Hopkins University School of Medicine's Center of Excellence for Ophthalmic Surgical Education and Training, says her program is an early adopter of the MicroVisTouch. "We have one; the University of Illinois at Chicago has one. We set one up at our sister institution in Saudi Arabia. I know that they're working on getting it distributed throughout China and India," says Dr. Sikder, who is also an unpaid advisor to ImmersiveTouch.

The MicroVisTouch can simulate the capsulorhexis, clear corneal incision and phacoemulsification steps of cataract surgery, and additional modules representing other steps are in the works. The MicroVisTouch doesn't come with a tangible set of instruments: instead, a robotic arm holds a handpiece "that looks kind of like an enlarged pen," according to Dr. Sikder; trainees hold that blunt-tip instrument to simulate the appropriate instrument for whatever

This article has no commercial sponsorship.

stage of surgery they are performing. In the VR immersion, the handpiece becomes a keratome, hook or forceps, for example, as the simulated procedure requires. One key difference between the MicroVisTouch and the Eyesi is that while the MicroVisTouch has a model head like the Eyesi does, the surgical trainee doesn't interact with it in the same way. It's there only for the trainee to practice proper hand placement on the patient's forehead and cheek as part of the surgeon's real-life posture.

Although MicroVisTouch users don't touch a physical representation of a patient in the same manner as Eyesi users, ImmersiveTouch claims that they experience haptic feedback—something new to the VR cataract surgery simulator market. "One could argue that microsurgery is largely visual," says Dr. Sikder. "How much are you really feeling when you're tearing a 15-micron membrane when you're doing capsulorhexis? But there are certain steps that do have tactile feedback. For example, when you're making a clear corneal incision in cataract surgery, that situation does offer tactile feedback in real life. To be able to simulate that adds value to the trainee's experience.

"It closely mimics the interaction you have with human tissue, so that you feel more or less resistance with certain maneuvers," Dr. Sikder explains. "Sometimes when you're making a clear corneal incision, there's a critical point where you'll go from feeling a lot of resistance to all of a sudden having no resistance. What we find in the operating room when training beginning residents is that they will often lose control of their instruments because that tension differential is so great. From that perspective, having the ability to train on a surgical simulator that allows that specific step to be practiced and finessed before going to the operating room is valuable."

The MicroVisTouch cataract surgery simulator has foot pedals that allow trainees to practice the phacoemulsification step.

Dr. Sikder and colleagues studied VR phacoemulsification simulators, and were able to validate the MicroVisTouch's ability to improve capsulorhexis skills,[3] but she acknowledges that validating the benefits to residents of having access to a VR simulator of any type is challenging. "What we're relying on, diffusely, is anecdote," she says, "and then some of the studies we are trying to do attempt to validate the existence of a skill improvement, or quantify how much a skill improved or determine which interventions led to the most improvement. In my current position, we're looking at technology, and we're trying to understand how we can assess surgical skills."

Eyesi

The Eyesi is the most prevalent of the commercially available VR surgical simulators in U.S. ophthalmic residency training programs. Its hardware consists of a model head on an adjustable table with a mechanical eye that is wired to a computer interface and a microscope. This setup allows the surgical trainee to assume a realistic posture. The Eyesi includes cataract surgical instruments and foot pedals. The mechanical eye has a series of holes in it for the trainee's instruments to enter. Entry into the eye generates a high-fidelity virtual image of the operative eye that is viewable through the microscope. Access can be superior or temporal.

Trainees can practice independently anytime, since the Eyesi is touchscreen activated and users can log in and get started immediately. Trainees can practice the steps in a divide-and-conquer phaco, with the exception of suturing. The latest software update, Eyesi 3.0, adds surgical scenarios including capsulorhexis on a milky-white cataract. The Eyesi platform can also be used with a vitroeretinal package for added flexibility. The Eyesi can play back simulated surgeries, allowing trainees to see what went right—or wrong.

Andrew Hendershot, MD, ophthalmology residency program director and clinical assistant professor of ophthalmology at Ohio State University's Wexner Medical Center, says that residents there use the Eyesi during all three years of training, most heavily during their second year. "The benefits of the Eyesi are far-reaching," he says. "Residents

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learn the foot controls in a no-stress environment, and they can work on posture and hand position. They also learn to work while looking through a microscope." He adds that the Eyesi allows for focused practice if a resident is struggling with a particular step of surgery. It also enforces the habit of learning incrementally even if a mentor is not present. "The Eyesi has a built-in curriculum that a resident must work through to unlock the next step," he says.

"One could argue that microsurgery is largely visual. How much are you really feeling when you're tearing a 15-micron membrane when you're doing capsulorhexis? But there are certain steps that do have tactile feedback."
— Shameema Sikder, MD

Use of the Eyesi has been shown in studies to correlate with real-life surgical skills in experienced cataract surgeons,[4] and one study[5] suggested that training with the Eyesi gave residents who trained on it shorter phaco times and fewer intraoperative complications in the OR.

Dr. Hendershot observes that the skills acquired on the Eyesi carry over into real-life procedures. "In terms of surgery," he says, "there is proven benefit in lower complications and shorter OR times."

Anecdotally, Dr. Sikder agrees with Dr. Hendershot that simulators deserve a place in the curriculum. Across a variety of medical and surgical specialties, simulator training has demonstrably increased trainee knowledge and skill, although the effects on patient outcomes are less marked.[6]

"I like making the analogy between the simulator and exercise equipment," she says. "If I asked you to hop on a treadmill and do half a mile, and then told you that you were ready for a marathon, you'd probably disagree, even though it's the same principle of putting one foot in front of the other. Simulators play a role, but in isolation they cannot really prepare you for the actual experience of performing surgery. That's why it's critical to have them as one element of a program that includes supervised wet-lab use, independent wet-lab use and review of surgical video. I think the use of simulators in that way is the next step in surgeon education." REVIEW

Dr. Hendershot disclosed no financial interest in the products discussed in this article. Dr. Sikder has no financial interest, but disclosed her role as an unpaid advisor to Immersive-Touch.

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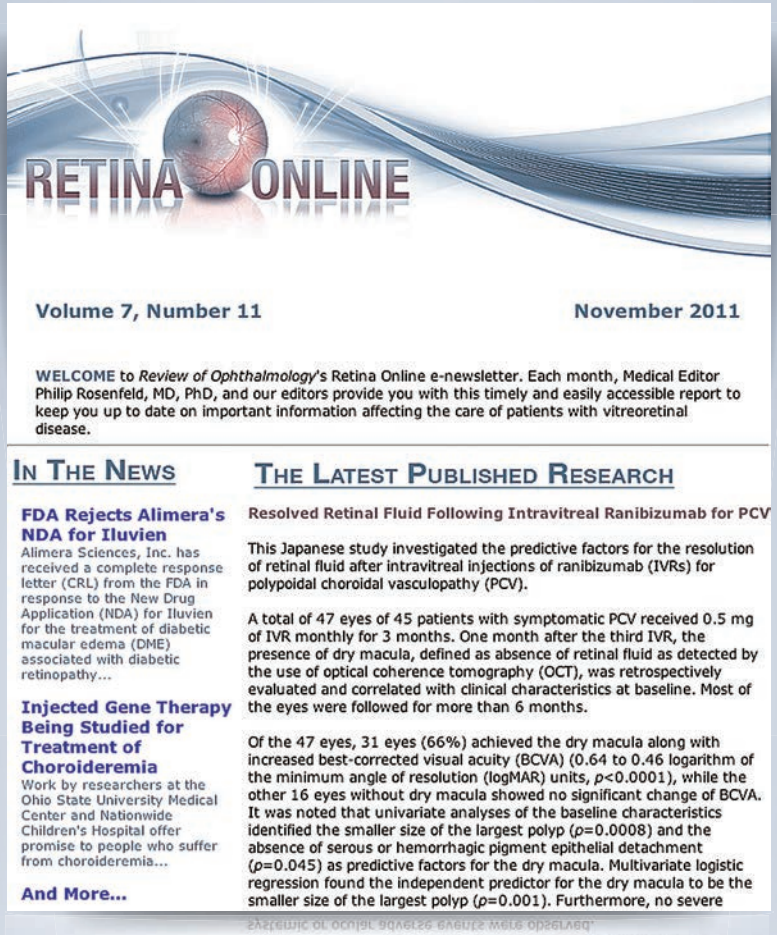

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WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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Resolved Retinal Fluid Following Intravitreal Ranibizumab for PCV

This Japanese study investigated the predictive factors for the resolution of retinal fluid after intravitreal injections of ranibizumab (IVRs) for polypoidal choroidal vasculopathy (PCV).

A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography (OCT), was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for more than 6 months.

Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution (logMAR) units, $p<0.0001$), while the other 16 eyes without dry macula showed no significant change of BCVA. It was noted that univariate analyses of the baseline characteristics identified the smaller size of the largest polyp ($p=0.0008$) and the absence of serous or hemorrhagic pigment epithelial detachment ($p=0.045$) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp ($p=0.001$). Furthermore, no severe

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Update: Is FLACS Better Than Manual Surgery?

Christopher Kent, Senior Editor

As the debate goes on, the evidence, and surgeons' experience, continue to be mixed.

One of the great debates in ophthalmology continues to be whether offering femtosecond-laser-assisted cataract surgery to your patients is worth the large capital investment in the equipment—not to mention asking your patients to pay extra for the procedure. Here, we offer an update on two important aspects of the debate: first, a sampling of recent published literature tackling this issue; and second, the thoughts of three surgeons with experience in both types of surgery regarding the pros and cons of FLACS; the questions surgeons are still asking; and why comparing FLACS to manual surgery is trickier than it may appear.

The Literature: Visual Outcomes

Here are some key studies that appeared in the past two years addressing the issue of whether FLACS produces better outcomes and/or fewer complications than manual cataract surgery. (Two meta-analysis studies are summarized at the end.)

First, the outcomes debate:

• A multicenter, case-control study conducted at multiple clinics in 18 European countries and Australia compared visual, refractive and adverse outcomes in 2,814 FLACS cases and 4,987 manual cases. Eyes were matched for preoperative corrected distance visual acuity, age and preoperative risk factors. For FLACS and manual, respectively:

— Seventy-two percent vs. 74.3 percent of eyes were within ±0.5 D of target.

— Postoperative logMAR CDVA in the two groups was 0.05 (6/6-3) for FLACS vs. 0.03 (6/6-2) for manual (zero=20/20); 96.3 percent vs. 97.1 percent had a CDVA of 0.3 (6/12) or better.

— One percent vs. 0.4 percent had a worse postoperative CDVA (five letters or more) at follow-up.

The authors also note that posterior capsule complications were observed in 0.7 percent of eyes (FLACS) vs. 0.4 percent (manual), and postoperative complications were seen in 3.4 percent vs. 2.3 percent, respectively.[1]

• A prospective, multicenter, comparative case series involving 1,876 eyes of 1,238 patients who underwent cataract surgery between January 2012 and June 2014 was conducted to evaluate visual outcomes after FLACS (988 eyes) vs. manual surgery (888 eyes). Among the findings:

— Postoperative BCVA was better after FLACS (20/24.5 vs. 20/26.4; p=0.0003).

— A greater proportion of FLACS cases achieved BCVA better than

20/30 (FLACS: 89.7 percent; manual: 84.2 percent; p=0.0006), and better than 20/40 (FLACS: 96.6 percent; manual: 93.9 percent; p=0.0077). However, manual cases gained more letters than FLACS cases (13.5 vs. 12.5 letters; p=0.0088), reflecting baseline BCVA differences.

— Mean absolute error was higher in FLACS than in manual surgery (0.41 D vs. 0.35 D; p<0.0011).

— The percentage of eyes within 0.5 D of target refraction was higher in the manual group (FLACS: 72.2 percent; manual: 82.6 percent; p<0.0001).

The authors concluded that FLACS did not demonstrate clinically meaningful improvements in visual outcomes over conventional phaco.[2]

• A 2016 single-center, single-intervention, prospective, comparative evaluation of 66 manual surgeries and 67 femto-assisted surgeries found:

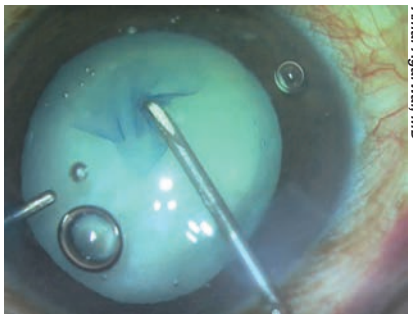
— Postoperative UDVA was 20/20 or better in 62.7 percent of FLACS eyes and 61.5 percent of manual eyes (p=0.075). Postoperative UDVA was 20/25 or better in 81.5 percent of FLACS eyes and 78.5 percent of manual eyes (p=0.042).

— in the FLACS group, 80.6 percent of eyes were within ±0.5 D of targeted refractive equivalent; in the manual group, 75.2 percent were (p=0.8732). A slight undercorrection trend was noted in the manual group.

The researchers also looked at a subgroup of patients receiving toric lenses. Average residual manifest cylinder in the femto surgery toric subgroup was -0.45 D; in the manual toric subgroup it was -0.50 D.[3]

• A non-randomized, single-surgeon, prospective, comparative cohort case series compared the outcomes of patients receiving toric implants between January 2012 and July 2014; 95 eyes received manual surgery and 323 eyes received FLACS.

— In terms of postoperative BCVA, 97.5 percent of the laser group achieved 20/40 or better, while only



Amar Agarwal, MD

Femto lasers are able to create very precise capsulorhexes, but they're occasionally incomplete, requiring manual intervention.

85.3 percent of the manual group did. However, this appeared to reflect preoperative differences; there was no significant difference in the amount of change. (The laser group gained 11 EDTRS letters; the manual group gained 10.3 letters [p=0.64].)

— Mean postoperative absolute refractive error was not significantly different (0.65 D for laser, 0.56 D for manual, p=0.18).[4]

• A prospective, randomized intra-individual cohort study of 100 patients compared visual recovery and refractive changes following FLACS in one eye and standard cataract surgery in the other. Six months postoperatively, 196 eyes were analyzed. The data showed that 90 eyes (92 percent) in the FLACS group and 70 eyes (71 percent) in the conventional group were within ±0.5 D of the target refractive outcome. (All eyes in both groups were within ±1 D of the target refraction.) In addition, FLACS yielded faster visual recovery and earlier stabilization of refraction.[5]

Complications & Safety

Here are some of the studies that focused on whether FLACS results in fewer complications:

• A prospective, consecutive, comparative cohort case series study conducted in Tasmania, Australia, compared the intraoperative complications and safety of FLACS (1,852 eyes) and conventional phaco surgery (2,228 eyes). It found:

— Anterior capsule tears occurred in 1.84 percent of FLACS eyes and 0.22 percent of manual eyes (p<0.0001).

— Anterior capsulotomy tags occurred in 1.62 percent of FLACS eyes.

— There was no significant difference in posterior capsule tears between the two groups (0.43 percent vs. 0.18 percent).

— The incidence of significant intraoperative corneal haze and miosis was higher in the FLACS group.

— Effective phacoemulsification time was significantly lower in the FLACS group (p<0.001).[6]

• A 2016 retrospective review compared rates of posterior capsule opacification in the first three months after surgery in 29 FLACS patients and 50 manual surgery patients. Seven of the 29 FLACS cases developed PCO requiring capsulotomy at three months; none of the manual cases required a capsulotomy during the same time period (p<0.05).[7]

• A 2016 paper reported the results of a retrospective case study done at two surgery centers in California, designed to compare YAG capsulotomy rates after manual vs. femto-assisted surgeries performed between August 2011 and August 2014. The data indicated that YAG capsulotomy rates were significantly lower in the femto-assisted group than in the manual group (p=0.04). The IOL material appeared to make a difference: Hydrophobic acrylic IOLs were associated with a lower capsulotomy rate than hydrophilic IOLs.[8]

• A 2016 prospective study conducted at a tertiary care ophthalmic institution compared manual to laser-assisted surgery in cases of white cataract. There were 40 eyes of 40 patients in each group. The data showed:

— The size of the capsulotomy/capsulorhexis was 4.9 ±0.1 mm in the laser group and 5.3 ±0.4 mm in the manual group (p<0.001).

— Mean circularity index was 0.996 ±0.003 in the laser group and 0.909 ±0.047 in the manual group ($p<0.001$).

— In the laser group, 52.5 percent of eyes had free-floating circular capsulotomies; 37.5 percent had microadhesions; 10 percent had an incomplete capsulotomy spanning one to two clock hours.

— Cases with release of white milky fluid had a higher incidence of residual adhesions ($p=0.003$).

— In the manual group, a multistep capsulorhexis was performed in 70 percent of the eyes.

— The data showed no difference in terms of visual outcomes or intraoperative complications.[9]

• A retrospective case series analyzed the vitreous loss seen in 3,784 manual surgeries performed by four surgeons between 2010 and 2012, and 3,371 femto-assisted surgeries performed in the following two years (2013 and 2014). The data showed:

— The rate of vitreous loss with exclusions was 1.17 percent in the manual group and 0.65 percent in the femto-assisted group; without exclusions, rates were 1.4 vs. 0.77 percent.

— Odds ratio analysis indicated that FLACS procedures performed in 2013 and 2014 were 1.6 times less likely (with exclusions) or 1.8 times less likely (without exclusions) to have vitreous loss than the manual surgeries performed earlier.

The authors conclude that converting from manual to FLACS resulted in a statistically significant decrease in vitreous loss.[10]

• In 2013, an interventional case series conducted in China studied 153 eyes that underwent FLACS and 161 eyes that underwent manual surgery to evaluate their comparative safety and effectiveness. The data showed:

— Effective phaco time was significantly lower in the FLACS group (14.05 vs. 23.65 seconds, $p<0.05$).

— The cumulative delivered energy was significantly lower in the FLACS group (4.78 vs. 8.82 percent, $p<0.05$).

— Corneal endothelial cell loss was significantly lower in the laser group than in the manual group at one month postoperatively ($p<0.05$).

— Postoperative anterior chamber flare was significantly greater in the manual group at day one and at one month ($p<0.05$).

— There were no severe surgical complications in either group.[11]

"Both techniques have benefits and limitations."
— Amar Agarwal, MD

• A prospective, consecutive, nonrandomized, comparative cohort study of 70 eyes undergoing FLACS and 54 eyes undergoing manual surgery during a six-month period compared the efficacy and safety of the two procedures. The data showed:

— Endothelial cell density in both groups decreased significantly postoperatively but remained stable during follow-up; ECD was lowest at one month. FLACS showed a greater, but not statistically significant, endothelial cell loss than manual surgery.

— CCT in both groups increased, reaching maximum thickness on day one and tending to decrease thereafter. No significant differences were found between the groups.

— Flare values following manual surgery were greater than following FLACS, reaching statistical significance at six months ($p=0.001$).[12]

• A nonrandomized, single-surgeon, prospective, comparative cohort case series conducted in Australia sought to evaluate the incidence of postoperative clinical cystoid macular edema associated with femto-assisted surgery using the Catalys Precision Laser System (Abbott Medical Optics) in 833 eyes, vs. manual surgery in 458 eyes.

There were seven cases of postoperative CME (0.8 percent) in the FLACS group, vs. one case (0.2 percent) in the manual surgery group. This correlated with a change in laser treatment speed due to a software upgrade, suggesting that retinal safety thresholds need further careful analysis.[13]

• A retrospective chart review at a private surgical center in Hawaii compared the complication rate of FLACS (273 consecutive eyes) and traditional phaco (553 eyes) during the first 18 months of FLACS use at the center. The overall complication rate for FLACS was 1.8 percent, vs. 5.8 percent for the traditional procedure. A majority of the surgeons (80 percent) had a lower complication rate while using FLACS.[14]

Meta-analyses

• A 2016 paper reported the results of a meta-analysis of 14,567 eyes from 15 randomized controlled trials and 22 observational cohort studies that compared the efficacy and/or safety of manual and femto-assisted surgery:

— There was no significant difference between FLACS and manual surgery in UDVA ($p=0.19$); CDVA ($p=0.26$); or mean absolute error ($p=0.57$).

— There was no significant difference in total surgery time ($p=0.07$) or corneal endothelial cell count ($p=0.07$) between the techniques.

— There was a significantly higher concentration of prostaglandins after FLACS ($p<0.001$).

— There were no significant differences in the overall incidence of complications between FLACS and manual surgery ($p=0.16$), but posterior capsular tears were significantly more common in FLACS ($p=0.005$).[15]

• A meta-analysis of nine randomized, controlled trials and fifteen cohort studies compared outcomes in

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2,861 eyes undergoing FLACS and 2,072 undergoing manual surgery. No significant differences were observed in the final CDVA or in surgically induced astigmatism. However, there were significant postoperative differences between the two groups favoring FLACS in endothelial cell loss percentage (at one week, one month and three months); in CCT (at one day, one month and at the final follow-up); in CDVA (at one week postoperatively); and in UDVA at the final follow-up. They also found significant differences in mean absolute error; effective phaco time; phacoemulsification power; and the circularity of the capsulorhexis.

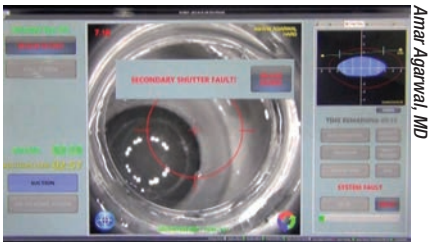
The authors conclude that FLACS is a safer and more effective method for reducing endothelial cell loss and postoperative central corneal thickening than manual surgery, and achieves better and faster visual rehabilitation and refractive outcomes (although there was no difference in final CDVA or surgically induced astigmatism).[16]

Surgeons: The Pros & Cons

Amar Agarwal, MD, chairman of Dr. Agarwal's Group of Eye Hospitals in Chennai, India (composed of more than 70 hospitals) has pioneered numerous surgical procedures, including bimanual phaco. He performs both FLACS and manual surgery, using either the Lensar or Victus laser system for FLACS. "There are pluses and minuses to both femto and manual phaco techniques, and it's important to note the strengths of each," he says.

Among the advantages FLACS surgeons cite:

• ***The laser centers and sizes the capsulorhexis very accurately.*** "It's an absolutely circular opening, and you can create the exact size you want and locate it exactly where you want it to be," says Dr. Agarwal. "That's especially useful when working with a mature cataract; creating a good 'rhexis



Amar Agarwal, MD

Different FLACS systems use different approaches to docking with the cornea. Loss of suction may occasionally occur.

can be difficult using the manual technique in that situation."

Sheri Rowen, MD, who practices at NVision Eye Centers in Newport Beach, Calif., and is a clinical assistant professor of ophthalmology at the University of Maryland, agrees. "Also, if the lens is subluxed or decentered, the capsulorhexis can be made more accurately for proper placement," she says. "In addition, when dealing with a white cataract, the capsulorhexis can be made more safely with the laser."

• ***The femto laser is very reliable for making arcuate incisions to correct astigmatism***. "When you're doing an astigmatic correction, you're making a partial-thickness radial incision in a particular axis," says Dr. Agarwal. "I think the laser does a much better job of that than a surgeon can do manually."

"Many surgeons don't correct astigmatism at all because they don't feel comfortable making arcuate incisions," notes Dr. Rowen. "With femto-assisted surgery, as long as you can mark the eye you can easily correct a diopter or less of astigmatism, which will leave you with a much happier patient. I've also had patients who needed a diopter more astigmatism correction than I could give them with a toric intraocular lens. The laser let me add that extra diopter of correction."

• ***It softens and fragments dense lenses, requiring less use of phaco energy inside the eye.*** " That's particularly beneficial in Fuchs' endothelial dystrophy patients," Dr. Rowen notes.

Concerns About FLACS

On the other hand, like manual surgery, using the laser has potential downsides:

• ***A laser capsulorhexis may not always be complete.*** "It's important to pay attention and complete the capsulorhexis manually if this occurs, because if you continue with the surgery, you'll cause a capsular tear," says Dr. Agarwal.

• ***A capsulorhexis made by the laser may be inherently less strong than a manual capsulorhexis.*** "The laser is making a string of many small dots that join together to create the capsulorhexis," Dr. Agarwal points out. "That doesn't mean a femto capsulorhexis is bad, but I believe this makes it inherently weaker than one made manually. Fortunately, at a practical level that's not a big deal; it doesn't matter much in most surgeries."

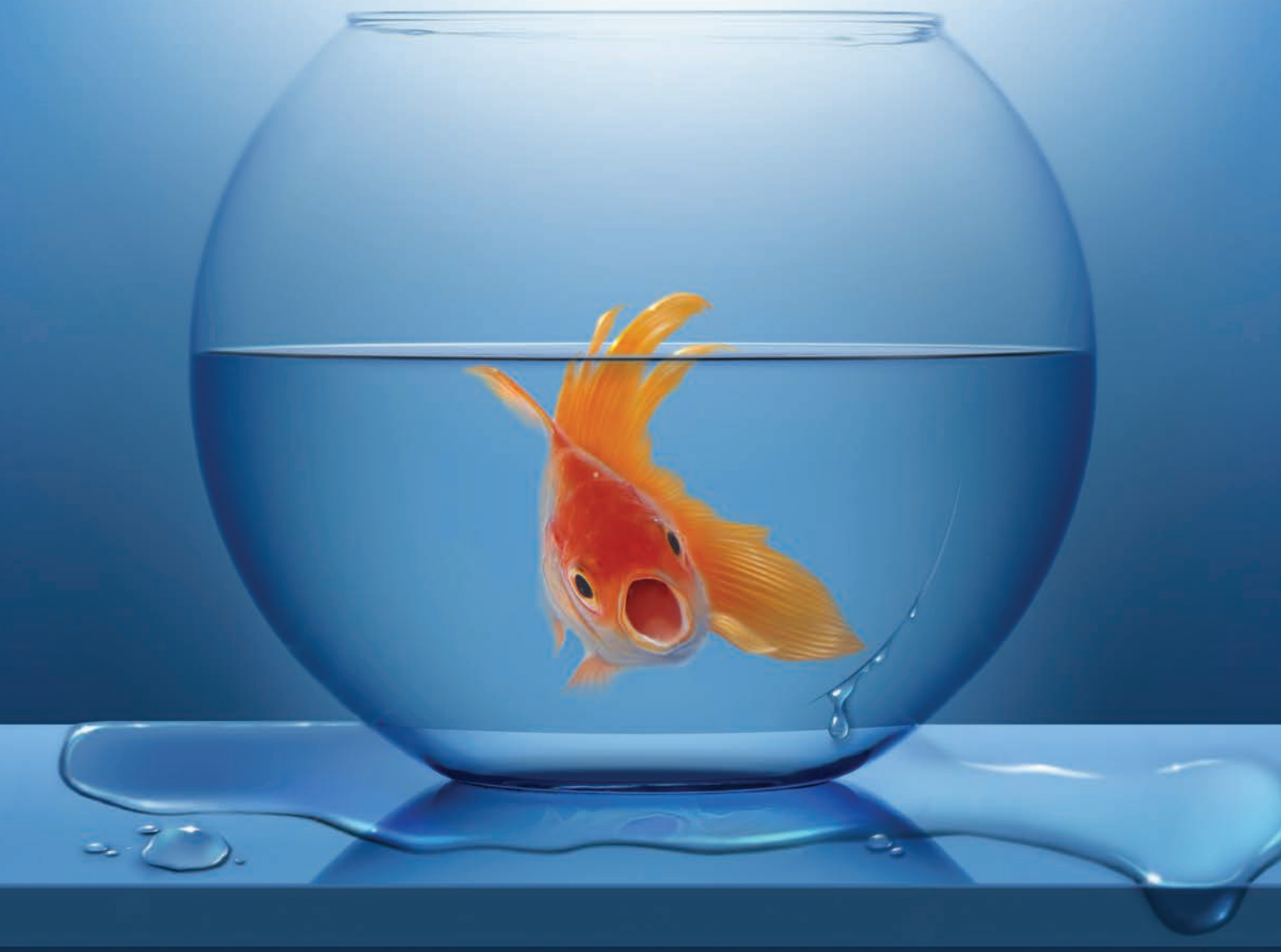
• ***A femto-generated bubble may break the posterior capsule.*** "A bubble is sometimes created when you're doing the emulsification of the cataract," says Dr. Agarwal. "When you remove the cataract, the bubble can break the posterior capsule."

• ***FLACS can trigger intraoperative miosis.*** "This can happen because the laser energy causes prostaglandins to be released," Dr. Agarwal explains. "For that reason, when you go in to remove the nucleus, you might end up with a small pupil. Fortunately, this doesn't matter too much if you're a good surgeon; you can redilate the iris using iris hooks or other devices."

Dr. Rowen says she routinely uses Omidria (Omeros) during these surgeries. "It does an excellent job of getting the pupil back to where it was and keeps it from coming down during the case," says Dr. Rowen. "I'm using the Malyugan ring less often to keep the pupil open since adopting Omidria."

• ***Some femto machines have a problem making a clear corneal incision.*** "A clear corneal incision has

Leaks still getting you down?



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to be full-thickness, and it has to be at an exact location," notes Dr. Agarwal. "Sometimes, when you try to make the incision with a femto laser, it doesn't go all the way through and you have to complete it manually. We recently had a case in which the femto system made the incision a little more towards the center of the cornea than we intended, creating a massive scar and leaving the eye with extra astigmatism. *(See photo, right.)* I believe you're better off making a clear corneal incision manually."

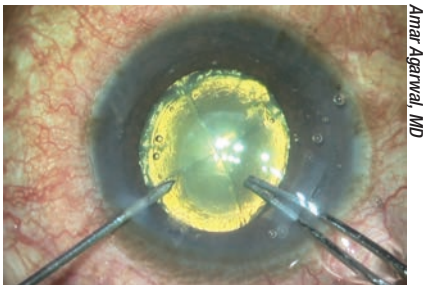
• ***Femto-assisted surgery can take significantly longer than manual cataract procedures.*** "It doesn't take more time to do the manual portion of the surgery," Dr. Rowen notes. "It's a question of throughput time, because the patient has to go to two different rooms."

She notes, however, that a solution to this problem may be on the horizon. "I recently tried the Ziemer system, and it allows the patient to stay in one room," she says. "The Ziemer is portable and can be brought right into the OR, and because of its design it can be used in a sterile manner. I was able to do a sterile laser procedure and then slide my chair to the side of the bed and start performing the rest of the surgery immediately. The time savings were pretty remarkable."

• ***A femto system is a big financial investment.*** "Clearly the cost of the laser is an issue," says Dr. Rowen. "You need to be making a profit every month to pay off the cost, and the technology could become obsolete after five or six years.

"The question is, do you want to have a state-of-the-art practice?" she continues. "Patients are coming in to our clinic asking for laser surgery. Part of this may be the result of other surgeons telling them that the surgery can be done with 'the laser or the blade,' but whatever the reason, they've heard about it and they want it."

• ***The patient has to pay more for femto surgery.*** "There's no question that the femto laser creates a good capsulorhexis, but that shouldn't be the only thing justifying the cost increase for the patient," says Dr. Agarwal. "The question is, are we giving the patient enough benefit to justify the cost? It's a very debatable point."



Amar Agarwal, MD

Some FLACS systems have difficulty making a clear corneal incision because of their docking technology. In this case, the incision ended up too far anterior, causing excessive postoperative astigmatism.

Some Key Questions

Surgeons debating the value of offering FLACS to their patients are asking a number of questions:

• ***Does femto-assisted cataract surgery change the outcome?*** Dr. Agarwal says that in his experience, using the femto laser does not improve outcomes. "Both manual and femto techniques give fantastic results," he says. "If you don't have any complications, I don't think there's any difference in the end result at all, and patients are happy either way."

• ***Are there fewer complications using the laser?*** Jeffrey B. Morris, MD, MPH, medical director of Morris Eye Group in Encinitas, Calif., says FLACS outcomes can be affected by the surgeon's learning curve, but the surgeons in his group haven't had to deal with too many complications. (Dr. Morris recently gave up performing cataract surgery, but still supervises multiple cataract surgeons in his group.) "We've had some incomplete capsulotomies, but that has improved over time with experience," he says. "On rare occasions we get little tags that prevent a free-floating capsulotomy, but those are easily dealt with at the time of surgery. To the best of my knowledge, we haven't had any ruptures of the posterior capsule, and all the fragmentations we've done were excellent. I don't believe we've had any radial tears since using the femto laser, which is a departure from our manual capsulotomy experience, where you can unintentionally dissect out to the equator. Although we haven't analyzed our data statistically, our surgeons believe they're having fewer complications with femto-assisted surgeries than they did with manual."

• ***Is femto better when implanting a premium lens?*** Dr. Agarwal says he doesn't find that he gets better outcomes using the laser when the implant is a premium lens. "The reason some say it's better is that the capsulorhexis made by the laser is very good," he notes. "But you can do a perfectly good capsulorhexis using a manual technique. In my experience it doesn't make any difference."

Dr. Morris disagrees. "Our laser gives us a choice between pupil centration and visual axis centration to make sure we get accurate placement of the IOL, which is important with a premium implant," he notes. "Since we switched to FLACS, we've had no problems with our premium IOLs. When we were doing strictly manual surgeries we got many more complaints about the premium implants."

"In our experience, a laser-created capsulorhexis does make a difference when implanting premium IOLs," says Dr. Rowen. "However, there aren't any studies that demonstrate significantly better premium IOL outcomes as a result of using FLACS."

• ***Is femto better if it's a complicated case?*** "Femto-assisted surgery is really great when you're dealing with a white cataract, pseudoexfoliation or floppy iris syndrome," says Dr. Morris. "You don't have to worry about com-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plications. We're able to make a perfect three-planar incision for the entry wound, and we haven't had any instances of iris prolapse in those cases."

• ***Is femto a good idea if the doctor isn't a master surgeon?*** "I don't buy that theory," says Dr. Agarwal, "because in the end every surgeon has to do a bit of manual surgery—even those using a femto system. It's true that the femto laser makes chopping easy, and the amount of energy used is much less. But you're still performing manual surgery."

Dr. Rowen disagrees. "If you're an average surgeon, and you don't always create a good capsulorrhexis, and you don't always chop the nucleus well, the laser makes everything easier—with the exception of cortical removal. If you're not good at chopping and you consistently create a bowl instead of nice segments, then the laser procedure would definitely make your surgeries go more smoothly."

"Proving" Superiority

In the debate about whether FLACS is actually better than manual, two important factors are often overlooked. The first is that different laser systems have different pros and cons, which means your comparison will be affected by the strengths and limitations of the femtosecond laser system you're using for the comparison.

"One issue that impacts the outcomes you achieve with the laser is which type of technology the instrument uses to dock with the cornea: immersion or non-immersion," notes Dr. Morris, who has used multiple systems. "Immersion technology allows very good imaging of the posterior structures, the lens and the capsulotomy, so, in theory, you get a slightly more accurate fragmentation and capsulotomy. However, the layer of water undermines the ability of the system to image the cornea well enough to make very precise incisions, astigmatic keratotomies or pockets for corneal inserts like the Raindrop. In contrast, non-immersion technology allows more accurate corneal imaging, but it's less accurate for imaging posterior structures, the capsulotomy and the nucleus for doing fragmentation."

Dr. Morris's practice uses the Bausch + Lomb Victus system, which allows the use of both technologies—immersion and non-immersion. "During the first part of the procedure we use immersion, which provides us with real-time imaging so we can watch the fragmentation taking place," he explains. "Once fragmentation and capsulotomy are complete, the water bath is eliminated and we have flat, surface-to-surface contact with the cornea. This allows excellent corneal imaging and very accurate incisions and astigmatic keratotomies."

Dr. Rowen agrees that different lasers have different strong points. "For example," she says, "the energy level and spot separation used when chopping the nucleus can make the segments easier or more difficult to remove. I've worked with several different lasers, and the difference in this respect can be very noticeable."

Dr. Rowen also notes that some docking systems are easier to manage than others. "The Lensar docks very easily," she says. "You can stand over the patient and put the first piece on; then you plug the laser into it. The Ziemer system is even easier. Some other systems are more challenging."

A second issue when comparing manual surgery to FLACS is that "proof" of superiority may be difficult or impossible to find. "Which data are you going to compare?" asks Dr. Morris. "When you look at manual surgery, which surgeons are you going to use as the basis for comparing complication rates? How do you equate the skill of the manual surgeon to the skill of the femto surgeon? How do you draw your sample to ensure that you're comparing apples to apples? You're always going to select your data according to some bias."

Dr. Morris adds that accepting something as "proof" is subject to personal bias anyway. "You can always take studies that some consider to be 'proof' and argue with them," he says. "In the case of femto-assisted surgery, having made such a large financial investment could also influence a surgeon's perspective. So I think that deciding whether FLACS is better than manual is ultimately going to come down to your experience. I don't think there will ever be conclusive proof."

The Last Word

"I think the bottom line is, both techniques have benefits and limitations," says Dr. Agarwal. "It all depends on the surgeon. Some surgeons are very comfortable with manual surgery and worry about the extra time and cost associated with performing femto cataract; others are very comfortable performing femto-assisted surgery.

"I always tell surgeons, do whichever type of cataract surgery you're good at and comfortable with," he concludes. "However, if you're going to use the laser, don't do it half-heartedly. Pay attention and be careful."

Dr. Morris says that in his practice, the laser has been worth the cost. "It's at least as safe as manual surgery," he says. "It's good for a practice to be involved in cutting-edge technology, and femto-assisted surgery is probably the future for ophthalmology. It can have a positive financial impact on a practice and pay for itself because you get higher rates of reimbursement. Ultimately, however, if you don't believe in it, you probably won't end up using it."

"If you're comparing standard, run-of-the-mill cataract surgeries in healthy eyes, I don't think you'll find any evidence that FLACS is better than manual surgery," says Dr. Rowen. "But there are plenty of studies showing that using the laser has advantages,

and I think it may allow a surgeon reaching his or her 60s or 70s to continue performing surgery instead of taking early retirement, because it assists with some of the more difficult and critical steps in the surgery."

"I haven't met a surgeon yet who wouldn't want the femto laser used if they had cataract surgery themselves, whether or not they use the laser in their own practices," adds Dr. Morris. "I think that's very telling." REVIEW

Drs. Agarwal, Rowen and Morris have no financial ties to any product mentioned.

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New Torics: What You Need to Know

Liam Jordan, Associate Editor

An in-depth look at the Symfony, ReSTOR and enVista toric lenses.

For years, surgeons outside of the United States have had access to more varieties of toric intraocular lenses than their U.S. counterparts. However, thanks to the recent approval of Alcon's ReSTOR +3 D multifocal toric and Abbott's Symfony, as well as a new lens in the pipeline, U.S. surgeons' options are multiplying. More options, however, means more information to sift through as you put these new lenses into practice. In this article, experienced surgeons offer their insights into the new lenses, both approved and on the horizon, focusing on the AMO Symfony, the ReSTOR +3 D multifocal toric and Bausch + Lomb's enVista toric, which is currently in trials.

AMO's Symfony Toric

The recently approved Symfony toric sets itself apart from similar lenses by being the only extended depth of focus lens approved in the United States. This hydrophobic, acrylic EDOF lens is able to achieve this extended-depth-of-focus through some unique design elements. The Symfony has a defractive grating on its face, similar to multifocal lenses, but has some significant differences. The ring structures have z-shaped echelette formations that elongate the focus area, rather than splitting and dispersing the light.

Jim Loden, MD, an ophthalmologist based in Nashville, provides some insight into the Symfony's design: "We're able to achieve an extended depth of focus through the manipulation of chromatic aberration," he says. The spherical shape of the lens and the hydrophobic acrylic material elongate the depth of field. By addressing the chromatic aberration, you maintain a higher modulation transfer function and decrease the loss of contrast sensitivity you usually find with traditional multifocal lenses." The design manipulates the chromatic aberration so that instead of dispersing the light, it helps collapse it into a tight region of focus, which improves contrast sensitivity.

The Symfony has four toric models to correct up to approximately 3 D of astigmatism at the corneal plane. Models ZXT150, ZXT225, ZXT300 and ZXT375 correct 1.03 D, 1.54 D, 2.06 D and 2.57 D of astigmatism at the corneal plane, respectively. "For treating more than that, we have the option of doing bioptics," says Dr. Loden. "I leave the patient with compound myopic

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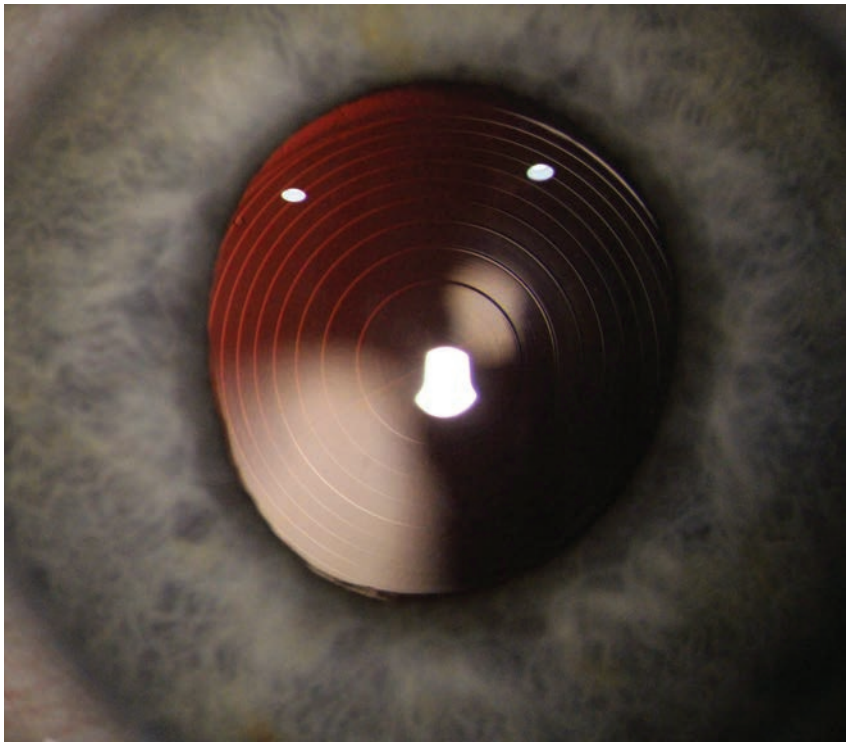
astigmatism; I intentionally leave him with nearsightedness in the IOL calculation. Then I can just do LASIK surgery to correct the rest of the astigmatism. Say someone has six diopters of astigmatism preop. You're going to get three diopters of it with the Symfony toric and correct 2.75 to three through the refractive surgery, depending on the calculation."

In terms of postop rotation, Dr. Loden claims that it's minimal. Because the Symfony lens is similar to the TECNIS Toric IOL, the FDA drew from the TECNIS Toric approval data, which reported that of the first eyes done with the toric lens, 97 percent had <10 degrees of rotation from baseline to six months. "I have presented that data, and I'm basically seeing zero rotation," he says. "I have not come back and repositioned a Symfony toric yet. For those saying the lens is more prone to rotate, I'm not seeing that at all." The same study reported more than 90 percent of eyes having ≤5 degrees of axis change between consecutive visits three months apart.

Sioux City, Iowa, surgeon Jason Jones, MD, offers these tips for reducing the risk of rotational issues. "The first is to have a very clean surgical experience without any zonular compromise and have the capsulorhexis overlap the optic for 360 degrees," he says. "Then, ensure you have complete viscoelastic removal from the posterior surface of the IOL. In my experience, I find that if I evacuate the viscoelastic from beneath the optic, it will disappear [from my view]. However, if I then rotate the lens 180 degrees and go behind the optic again, I'll sometimes find a very small amount of viscoelastic remaining.

"In addition, though you of course leave the eye nicely closed and secure in terms of the wound, you might want the IOP to be a little lower than with a non-toric lens," Dr. Jones adds. "This is so you don't hyperinflate the capsular bag and the anterior segment, and instead have it 'collapse' around the haptic peripherally, if you will.



The Symfony has four toric models to correct up to approximately 3 D of stigmatism at the corneal plane.

"If you want to avoid a rotational issue, I'd look into a capsular tension ring," he continues. "The first option along these lines would be a regular CTR that most surgeons are familiar with. This will help ensure the capsular bag is symmetrically expanded and that there's no ovalization of the peripheral capsule. Ovalization can permit the lens to rotate, and this helps prevent that. The other strategy, though I don't use it routinely, is to use a Henderson CTR. This device has undulations in the ring structure and it, theoretically, provides an interface for the haptics to interact with, peripherally, thus preventing a rotational problem. The last strategy—which most surgeons probably won't want to employ—is to do some form of optic capture," he continues. "In some circumstances you can consider a reverse optic capture in which the haptics are in the bag and the optic is prolapsed through the anterior capsulorhexis. I tend to avoid this in the Tecnis single-piece family because the optic has fairly thick peripheral structure and has a squared-off anterior and posterior edge, and I want to avoid any potential iris chafe. Other single-piece acrylic lenses from other manufacturers might be more agreeable to this strategy, however. For the Tecnis monofocal toric lenses, I've also employed optic capture through a posterior capsulorhexis, both secondarily in patients who experience rotation and in primary cases in which I want to avoid rotation. Though this ensures no postop rotation, it's not for the faint of heart, since you must be willing and able to perform a posterior capsulorhexis."

To aid in the implantation of the

new toric Symfony, Abbott offers an online calculator. Visit it at https://www.amoeasy.com.

Alcon's ReSTOR +3 Multifocal Toric

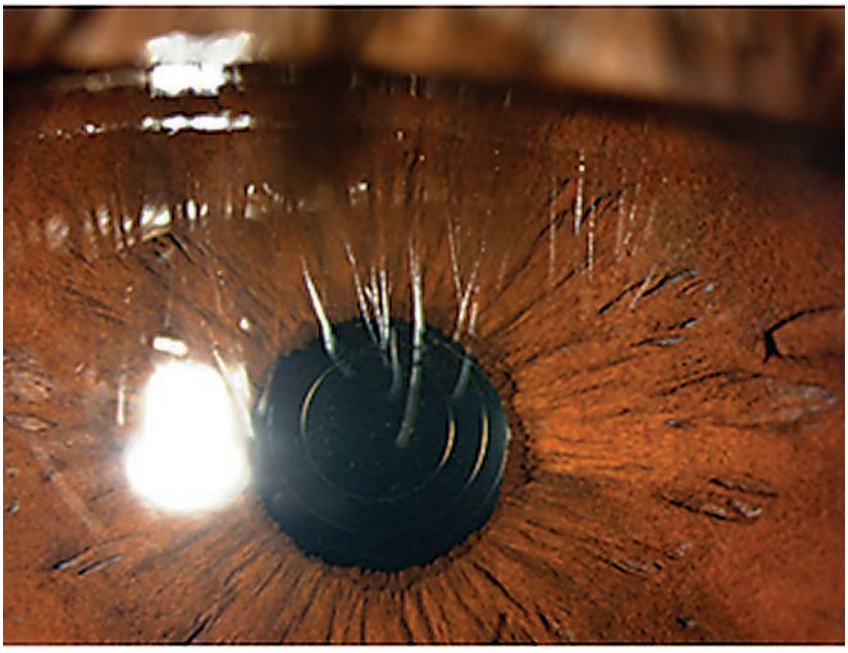
The ReSTOR +3 D Multifocal Toric has the distinction of being the first toric multifocal approved in the United States, winning approval in late December 2016.

The lens is a foldable, hydrophobic acrylic. The diffractive, multifocal optic is on the anterior surface of the lens, with the toric component incorporated on the posterior surface. Since the lens is biconvex and foldable, it can be implanted through a relatively small incision. It's available in four models for correction of astigmatism from 0.75 to 2.82 D at the corneal plane.

Suresh Pandey, MD, of Kota, India, describes the design of the toric ReSTOR. "The new lens is built on Alcon's AcrySof platform and is designed to provide cataract patients that have astigmatism with a surgical option that delivers quality vision at all distances," he says.

Regarding implanting the ReSTOR multifocal toric model, Dr. Pandey provides some surgical pearls. "A meticulous surgical technique is necessary," he says. "Based on a toric IOL calculation, we prefer to make a clear corneal incision at the steep axis to minimize or eliminate pre-existing astigmatism, which we factor into the amount for the toric lens to correct. The capsulorhexis should be circular, well-centered and slightly smaller than the IOL optic diameter to maximize the effective lens position. Because it is a multifocal IOL, it should be implanted in the capsular bag. Once implanted, the surgeon should be careful to remove all viscoelastic behind the IOL optic."

Dr. Pandey also provides some insight into managing intraoperative complications. "If the posterior capsule is torn, the surgeon should try to convert the tear to a circular posterior capsulorhexis," he says. "Toric and multifocal toric IOL implantation shouldn't be attempted in the capsular bag in the presence of a posterior capsulorhexis. If a posterior capsulrrhexis can't be achieved, then sulcus implantation of a three-piece, monofocal IOL with optic capture in the bag behind the anterior capsulorhexis can be attempted. Don't forget to adjust the IOL power in this event."



This postop image shows a clear cornea and the ReSTOR multifocal toric IOL successfully implanted in a 45-year-old patient who underwent refractive lens exchange.

In terms of postop complications, Dr. Pandey says rotation is not too much of an issue, though he does recommend follow-up appointments at least three months apart to monitor rotational stability. Because of its multifocal design, the lens is more prone to halos and glare, however. The data from the clinical study[1] demonstrates that the highest rate of "severe" reports of visual distortions at one year was for halos, at 7.5 percent. In terms of glistenings, 95.7 percent and 96 percent of subjects had no observation of glistenings in the first and second eye, respectively. None of the observed glistenings were reported as clinically significant by the implanting surgeons.[1] "The problems of glare and halos during night-time are typically minimal with the modern toric multifocal IOL design," Dr. Pandey says. "Refractive surprise after implanting a toric multifocal can also be managed with LASIK or piggyback IOL implantation." The data from the FDA trial demonstrates that 94.2 percent (first eye) and 93.9 percent (second eye) of the subjects had rotation of five degrees or less between two consecutive visits.

In the trial, 97.2 percent of first and second eyes had less than 10 degrees of rotation from surgery to 12 months. The mean absolute difference between the achieved lens axis orientation at surgery and at 12 months was 2.7 ±5.8 degrees in the first operative eyes and 2.2 ±2.7 degrees in the second operative eyes. Furthermore, the mean actual dif-

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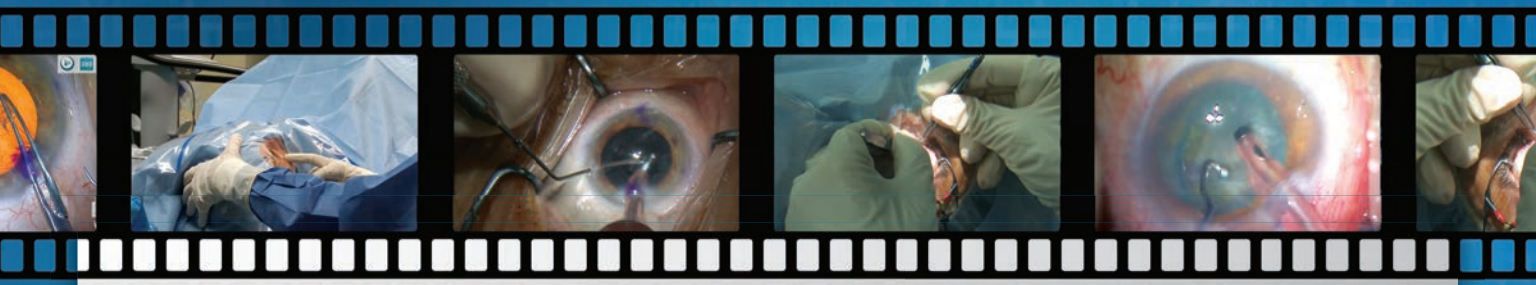

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Episode 15:
"Fluidics, Fluidics, Fluidics"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
In this issue, I discuss and demonstrate the synergism of high IOP and high vacuum settings during phacoemulsification.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

Welcome to the second year of Mackool Online CME! With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

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ference between the achieved lens axis orientation and the achieved axis placement at surgery (either positive or negative) was ≤1.0 ±6.3 degrees in the first and second operative eyes at all postoperative visits.

Alcon also offers a toric lens calculator. View it at http://www.acrysoft-oriccalculator.com.

Bausch + Lomb's enVista

Not approved in the United States—but in clinical trials—Bausch + Lomb's enVista toric IOL is in the pipeline, with the company hoping it'll be approved within the year. The enVista toric IOL is made of a hydrophobic acrylic material, and is designed to be kept in isotonic saline in its packaging so that it emerges with the same tonicity as the aqueous. The company says that this prevents the mechanism that results in glistenings.

Mark Packer, MD, a surgeon from Boulder, Colo., describes the toric models that the enVista offers. "There are three steps similar in magnitude to the the AcrySof toric," he says. "It's 0.9 D, 1.4 D and 1.93 D in terms of the astigmatism it corrects at the corneal plane."

Bausch + Lomb's enVista toric IOL.

When discussing the postop results in terms of visual acuity and corrected astigmatism, Dr. Packer says, "It does quite well," referencing a 2015 study[2] that measured the postop results of the enVista. According to the study, 90.5 percent of eyes implanted with the enVista toric IOL showed less than five degrees of rotation. More than 10 degrees of rotation was observed in 9.5 percent of patients with the enVista toric.[2] In terms of uncorrected distance visual acuity, 80 percent of the enVista cases saw 20/25 or better postop, and just under 40 percent saw 20/20 or better. Same thing for correction of astigmatism. It decreased the average astigmatism from 1.89 D preop to 0.41 D postop.[2]

Dr. Packer also offers a pearl to ensure good surgical outcomes. "One of the things with the enVista material is that it unfolds a little more slowly than the other torics," he says. "You have to wait 30 seconds when you implant the lens to let it unfold. We learned pretty early on that if you're in a hurry and you get up from the operating table before the lens is in the capsule, it will rotate when the patient sits up. It hasn't contacted the capsule—it's still a taco shape. So, given that you will wait the 30 seconds because you believe in good outcomes, then the mean rotation is in the realm of two degrees. Dr. Packer also highlights the importance of follow-up appointments. "Rotation generally occurs between the end of surgery and the next visit," he says. "That's the most important time point, which is why you must let the lens unfold all the way."

Upon the enVista's approval in Europe, Bausch + Lomb reported that the trials showed that 91 percent of patients had ≤5 degrees of rotation from postop to six months. The mean rotation at six months was 3 degrees. Bausch + Lomb also noted that no glistenings were detected with the enVista lens at any time during a two-year prospective study of 172 eyes.

Regarding the timeline for the enVista's approval in the United States, Dr. Packer believes that the approval is imminent. "The FDA study is complete, and the submission is in process," he says. "Bausch + Lomb would probably be expecting approval sometime this year. The company's monofocal enVista has been approved for several years, which is the same lens without the toric element, so I would assume the approval will be happening soon." REVIEW

Dr. Loden is a consultant for AMO and was paid as a part of the Symfony FDA trials. Dr. Jones has consulted for Abbott and was an investigator in the Symfony FDA trial. Dr. Pandey reports no financial interest in any products or procedures discussed in this article. Dr. Packer is a consultant for Bausch + Lomb.

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Going Dropless, Being Careful

Kristine Brennan, Senior Associate Editor

Dropless or "less-drops" cataract surgery can be less of a hassle for you and your patients. Here's how to approach it with care.

"The intracameral approach is something that doctors in the United States are slowly but surely transitioning to, with good reason," claims Sydney L. Tyson, MD, MPH, attending surgeon at Wills Eye Hospital and CEO of Eye Associates SurgiCenter of Vineland in New Jersey. Dr. Tyson and others of his ilk point out that traditional infectious endophthalmitis and CME prophylaxis after cataract surgery consists of multiple bottles of topical drops that can be expensive and hard to keep track of for patients. They say that perioperative antibiotic and steroid injections can help decrease compliance concerns and costs for patients, but note that making the switch requires time and consideration.

A look at the dropless/less-drops approaches employed by three surgeons follows, together with a discussion of the benefits, risks and regulatory environment surrounding the dropless and less-drops trends.

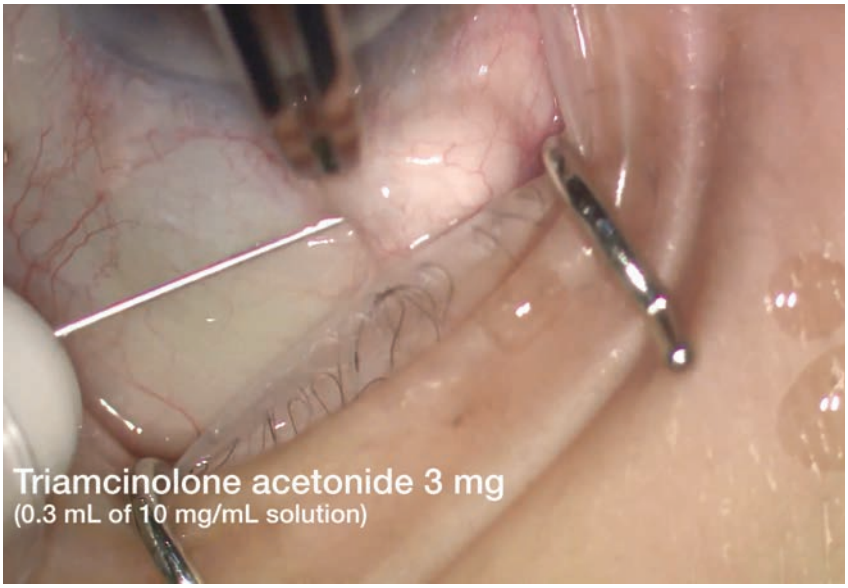
Why Go Dropless?

Post-cataract surgery drop regimens are notoriously labor intensive for doctors and staff as well as their patients, who tend to be older and more prone to physical and cognitive challenges that may make opening bottles, instilling drops and remembering dosing regimens a struggle. "It was confusing and detrimental to compliance when we had three separate bottles," says Asim Piracha, MD, medical director of John Kenyon Eye Center in Louisville, Ky. "Patients had to make a bunch of check marks on sheets of paper, and they would still get confused." Dr. Tyson adds that the drop burden on his patients created a disproportionate call volume for his staff. "Even with all the effort we'd put forth with counseling and schedules, our staff would continually get calls to answer patient questions about drops, not to mention refills. We'd be inundated: I'd say about 70 percent of our calls were related to postoperative drops," he says.

Neal H. Shorstein, MD, of the Departments of Ophthalmology and Quality at Kaiser Permanente, Walnut Creek, Calif., believes topical ophthalmic therapy after cataract surgery might open avenues to the very infections it's designed to prevent, via contaminated dropper bottles and touching of the eye. "Perhaps the less patients touch their eyes, the less chance there is of manipulating or burping fluid into the wound, allowing bacteria to enter,

which may lead to endophthalmitis," he says.

Practical difficulties and theoretical risks aside, the financial burdens topical eye drops pose to Medicare, Medicaid and patients are not insignificant. A 2015 report commissioned by Cataract Surgeons for Improved Eyecare and partially funded by Imprimis Pharmaceuticals, a maker of several dropless options,[1] estimates that allowing patients to elect and pay for dropless cataract surgery (estimated to be $100 per prescription) would save Medicare and Medicaid approximately $7.1 billion between 2016 and 2025.



Neal H. Shorstein, MD

Subconjunctival triamcinolone injection. This method of steroid injection is painless and does not induce postoperative floaters. Although the risk of patient response necessitating removal of the steroid is small, subconjunctival injection leaves the steroid accessible.

Applying Evidence to Practice

Injections at the time of cataract surgery have been used for years to prevent infection.[2] A commercial, single-dose cefuroxime preparation, Aprokam (Laboratoires Théa, Clermont-Ferrande, France), is available in Europe specifically for intracameral injection. The European Society of Cataract & Refractive Surgeons published a study[3] demonstrating the superiority of intracameral cefuroxime for postoperative infection control that prompted worldwide notice in 2007. This prospective, randomized trial looked at endophthalmitis risk factors and the efficacy of 1 mg of cefuroxime diluted with 0.1 mL saline injected intracamerally in 16,603 patients in facilities in nine European countries. The use of cefuroxime injections was associated with a nearly fivefold reduction in endophthalmitis risk.

When he noted an uptick in endophthalmitis cases in Kaiser Permanente's Diablo service area in northern California, Dr. Shorstein looked to the ESCRS study. "In our department in 2007, we had a slightly higher incidence of endophthalmitis. We were doing about 3,000 surgeries a year at the time, and we noticed a few more infections than in previous years. That's what prompted us to look in the literature and identify areas where we could address that," he says.

Dr. Shorstein developed an antibiotic protocol dating from 2007 that was ultimately adopted throughout the Kaiser Permanente facilities in northern California. It includes injection of either cefuroxime or moxifloxacin after cataract surgery. "We inject 1 mg in 0.1 mL through the sideport incision at the end of the case. There was a recent report[4] showing that using cefuroxime for stromal hydration keeps more drug around the wound site for a much longer period, up to 24 hours," he says. "So a few of us inject a little bit of antibiotic into the cornea itself by stromal hydration, where it helps seal the wound, and apparently keeps the antibiotic at the wound site for many hours after surgery."

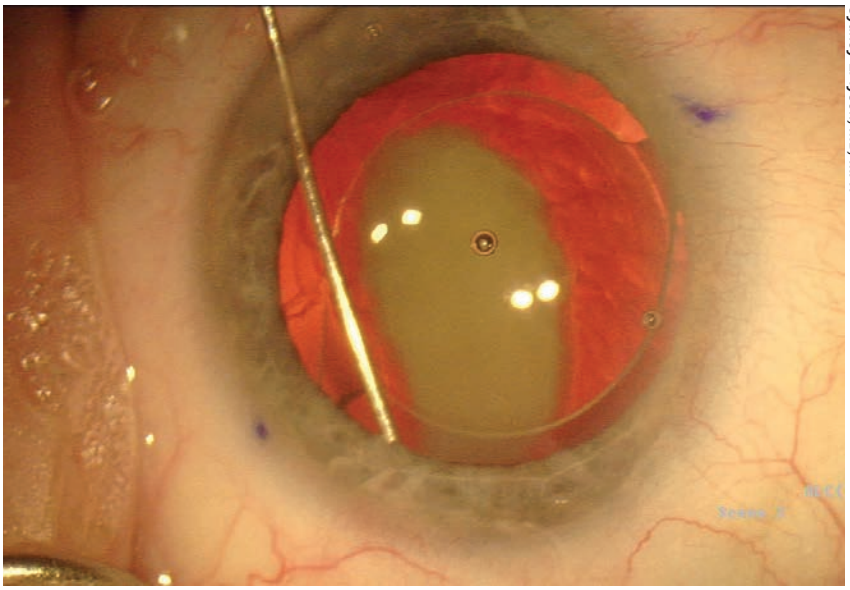
For his drop-free approach, he follows the intracameral antibiotic injection with subconjunctival triamcinolone. "In about 2008, following some successful reports in the literature, a small group in my department started to inject subconjunctival triamcinolone and stopped using topical drops of any kind after cataract surgery. We subsequently studied outcomes and found that it worked very well," he says. "We've been doing pretty much the same thing since then."

Dr. Shorstein and colleagues evaluated the results of making intracameral antibiotic injections the standard of care in their service area over time. Their 2013 study[5] showed that the incidence of endophthalmitis dropped from 3.13 per 1,000 during the initial 2007 and 2008 implementation period, to 0.14 per 1,000 in 2011, the last period reviewed. A 2016 comparative study[6] of the records of 312,246 cataract procedures on 204,515 patients from 2005 to 2012 at Kaiser Permanente California showed that intracameral antibiotic injection (with an endophthalmitis incidence of 0.04 percent [0.4 per thousand]), was superior to topical antibiotic alone, (with an endophthalmitis incidence of 0.07 percent [0.7 per 1,000]), and that antibiotic drops didn't confer

any additional benefit when instilled after intracameral injections.

Louisville's Dr. Piracha has been using a mixed dropless and less-drops protocol for more than three years. The antibiotic injection regimen is derived from the 2007 ESCRS study protocol. "If our patients don't have a cephalosporin allergy, we'll use cefuroxime intracameral injections on everybody at the conclusion of the case. We also do sub-Tenon's triamcinolone," he says. Dr. Piracha's patients also get a postoperative combo drop consisting of moxifloxacin, prednisolone acetate and bromfenac for added coverage. "Some people still get the three separate prescription bottles," he says, "but most will go with the bottle that's compounded, which is around $50, cash only, for all three medicines. We can usually use the same bottle for both eyes, so most of our patients end up paying just $25 per eye. It's easy because they use just one bottle four times a day for four days, tapering down over a four-week period."

Dr. Tyson uses a transzonular intravitreal injection of Tri-Moxi-Vanc (Imprimis Pharmaceuticals, San Diego), a proprietary compounded mixture of triamcinolone, moxifloxacin and vancomycin, at the end of cataract surgery. He considers his dropless technique a "practice growth-builder" that attracts patients. "Before I had a compounded material I felt comfortable with, I would use intracameral Vigamox (Alcon) straight out of the bottle because it was preservative-free, and I would put it into the anterior chamber. I used that for endophthalmitis prophylaxis, but it really didn't solve the issue of inflammation. I would always have to add a drop of some kind for inflammation, or give a posterior sub-Tenon's injection of a steroid if I wanted my patients to be entirely drop-free," he says. "I started with Imprimis around November of 2013.



Sydney L. Tyson, MD, MPH

Transzonular intravitreal injection with Tri-Moxi-Vanc. The triamcinolone plume is clearly visible, and patients may notice floaters for about a week. Although there is a small risk of IOP spike, the steroid remains active in the eye for several weeks postop to fight edema.

We took a gradual approach. I still used drops until I was really sure of my technique. When you put the medicine properly into the posterior chamber, you know it. But in the beginning you're a little tentative in going through the zonules, so you might not get it all in. Within 15 to 20 patients or so, you really pick up on it, but until then you want to make sure you're covered adequately. So there was a bit of a transition, as there should be with any new technique or technology," Dr. Tyson observes.

The transzonular intravitreal approach does carry a risk of zonular damage and consequent capsular bag instability, which in cataract surgery can cause decentration of the IOL; this must be weighed against the remote but serious risks of retinal detachment and hemorrhage with pars plana intravitreal injection.[7]

Dr. Tyson differs from Dr. Shorstein and Dr. Piracha in electing to do an intravitreal injection, intended to maximize the activity of the antibiotic. "The ESCRS study was a milestone, showing that there was a fivefold reduction in infectious endophthalmitis by putting intracameral cefuroxime, a second-generation cephalosporin, into the anterior chamber. Putting it into the anterior chamber works," he says. "Then the Shorstein study in 2013 showed a 22-fold reduction in endophthalmitis, and it really didn't matter which antibiotic you used when you placed it intracamerally. The problem with an intracameral approach is that there's a turnover of fluid in the anterior chamber every two to four hours. The vitreous has a much slower turnover and acts as a depot. This has not been studied clinically and there is no peer-reviewed data on it, but theoretically, there's a 12-hour turnover when you put antibiotic into the area where you're most concerned about bugs: the vitreous. You lay that stuff in there, and it gets slowly resorbed and released over at least a 12-hour period."

Study Your Own Patients

In addition to inferring his ideal injection approach, Dr. Tyson studied his clinical outcomes to help ensure safety and improve results with Tri-Moxi-Vanc. Of a retrospective review of 1,541 procedures[8] at his facility us-

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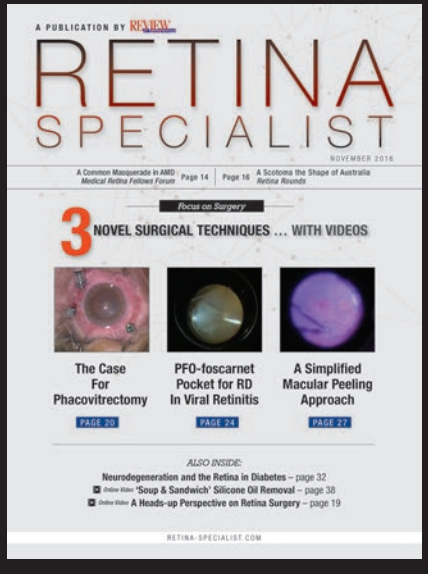

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ing injected Tri-Moxi-Vanc, he says, "We had very few pressure spikes: We saw less than one percent, and all of those patients were easily handled with medication, although many did not even require it. It was a transient phenomenon."

Dr. Tyson's study reports that breakthrough inflammation at postop days 14 through 21 was 9.2 percent, but that the proportion of those instances of inflammation was smaller during the second half of the study period. "As time has gone on, I've recognized that patients who have darker irises tend to have more of a rebound iritis phenomenon, so we give just a little bit more Tri-Moxi-Vanc. That seems to have reduced the rebound iritis by almost 50 percent in those patients," he reports. "We now realize that there are things you can do to reduce the incidence of even the few issues that might happen." Although the visually significant CME rate at days 14 through 21 was 2 percent, he noted that 35 percent of the patients who developed CME had had a previous episode of iritis, and so he began to start his postop iritis patients on a preventative nonsteroidal. "That's the beauty of looking at your data," he says. "We know who's going to possibly have issues, so we try to be a little preemptive. You can use either a less-drops preparation, or you can use just use a nonsteroidal." Another group at risk of CME consisted of patients with epiretinal membrane, so they, too, were started on a postop nonsteroidal in addition to the injection.

All three surgeons have made dropless and less-drops procedures work for them by staying alert to patterns in the literature and their own clinical experience, and then adjusting their protocols accordingly. Dr. Piracha says, "It's come down to four or five iterations in the last couple of years, trying to find the best and the safest." Although his practice tried intravitreal Tri-Moxi, a proprietary mix of triamcinolone and moxifloxacin from Imprimis, they saw inflammatory reactions within their first 1,000 cases that prompted them to switch to separate cefuroxime and triamcinolone injections.

With intravitreal steroid, floaters do occur, but Dr. Tyson says that they are short-lived and haven't diminished the "wow factor" of cataract surgery for his patients. "Patients experience a few floaters here and there, but we warn them ahead of time so they're not freaked out by them, and they're gone in about five to seven days." He adds that using an inferonasal approach with the TMV helps prevent patients from perceiving any floaters in their central vision.

Assessing the Risks

When mixing agents and injecting them into patients' eyes, the potential for damage from human error is always present. One adverse event reported in the literature was an outbreak of toxic anterior segment syndrome among 12 cataract patients who were inadvertently injected with Moxeza (Alcon), a brand of moxifloxacin containing preservatives, instead of Vigamox.[9] Compounding your own agents entails the risk of contamination or dilution mistakes. "Dilutional error from compounding drugs has been reported in the literature that has caused macular edema and toxic anterior segment syndrome," notes Dr. Shorstein.

Dr. Piracha relies on an FDA-compliant outsourcing facility that formulates medications per patient-specific prescriptions. "We don't even want to come close to messing with the rules," he says. "Each patient has his or her own single-use vial of antibiotic made up in sterile packaging. The compounding pharmacy makes our cefuroxime; they also make preservative-free triamcinolone for each patient, individually wrapped for a single use."

"We feel that since there is no FDA-approved manufactured drug that is available—which would certainly be our first choice—sourcing antibiotic for intracameral injection from an FDA-registered compounding facility is a good second choice," adds Dr. Shorstein. Like Dr. Piracha's practice, Dr. Shorstein's department gets its postoperative medications directly from a compounding pharmacy that is registered with the FDA pursuant to Section 503(b) of the Drug Quality & Security Act of 2013, which among other things, subjects compounders to FDA inspections. The Imprimis injectables that Dr. Tyson uses also come from an FDA-registered facility. Referencing the 2012 meningitis outbreak traced to steroids mixed at the New England Compounding Center in Massachusetts that killed 64 and sickened over 700 others, Dr. Tyson says of the response to the resulting enhanced legislation, "It's really very remarkable how some of these compounding facilities have come to the forefront in addressing safety to make us feel a whole lot more secure about using them."

The risk of IOP spike when injecting a steroid initially prompted Dr. Shorstein to go beyond simple informed consent. "Early on, we advised our patients that there were no FDA-approved drugs for endophthalmitis or CME prophylaxis, and that the steroid injection could increase their intraocular pressure, and if that occurred, we would either need to add drops for a short time or excise the depot of triamcinolone," he recalls. "Then my research team published a study recently.[10] We looked at over 16,000 eyes in my department and looked at three groups: One group got topical steroid after surgery; one group got topical steroid and nonsteroidal anti-inflammatory

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1. Bala C, Xia Y, Meades K Electron microscopy of laser capsulotomy edge: Interplatform comparison. *Journal of Cataract & Refractive Surgery*, Vol. 40, Issue 8, p1382–1389

drops in addition to the steroid; and the third group were the patients who just got the injection of triamcinolone. We found there was no difference in CME in the groups that had topical steroids or the group that got the injection. There was no difference in postoperative iritis diagnoses," he says. The study also showed that the percentages of eyes with intraocular pressure spikes above 30 mmHg were about the same in patients who got subconjunctival injections as in those who got topical prednisolone drops. "So I really stopped the additional counseling to individual patients after that study, other than including in their preoperative educational materials that they would be receiving injection and there was a small risk of increased intraocular pressure," Dr. Shorstein says.

Regarding Vancomycin

Dr. Shorstein's department will rarely use vancomycin, generally only in patients with known penicillin, cephalosporin or fluoroquniolone allergies. He acknowledges that for certain immunosuppressed patients, or those who are already colonized with MRSA, vancomycin injection may be beneficial. Dr. Piracha doesn't use vancomycin at all. Recent studies linking vancomycin to postoperative hemorrhagic occlusive retinal vasculitis (HORV),[11] a rare condition characterized by initial painless blurred vision, retinal vascular occlusion and hemorrhage leading to profound vision loss, have given doctors pause. "In general, we respect the recent reports that have shown the devastating loss of vision in patients who are injected with vancomycin, and at Kaiser Permanente Northern California, we aren't routinely injecting it," says Dr. Shorstein.

Dr. Tyson initially responded to reports associating vancomycin with HORV by eliminating it from his injections. "I switched to Tri-Moxi for a little bit, then switched back to TMV," he says. "HORV scares you, but it's just not worth it to me, for something that seems idiosyncratic from a statistical standpoint, to potentially do the patient a disservice by possibly not treating those gram-positive bugs." He also notes that no cases of HORV have been reported using the product he injects at the conclusion of cataract surgery.

Vancomycin has long been considered an antibiotic of last resort, and its use hasn't been encouraged for cataract surgery.[12] Dr. Tyson doesn't believe that injecting vancomycin into the eye is a contributor to vancomycin resistance, however. "Either intravenously or as a drop, we might only partially kill bugs and then those bugs could regenerate," he says, "but inside the eye we have a closed system. It's highly unlikely that we'd create a

resistant bug by putting it inside the eye."

Regulatory Dilemmas

The use of intracameral prophylaxis after cataract surgery is ubiquitous in Europe, and even jointly supported by governmental recommendations and national ophthalmological societies in France and Denmark.[13] Although American surgeons may believe that dropless approaches are safe and effective, they may also be deterred by the lack of an FDA-approved agent, as well as Medicare and Medicaid regulations that compel them to absorb the cost of the injections.

To date, the FDA has received no applications for an antibiotic endophthalmitis preventative for injection. Given that the incidence of endophthalmitis after cataract surgery is estimated to be approximately 2,000 eyes among some 3 million cataract surgeries annually in the United States,[13] the costs of recruiting patients for a powerful randomized controlled trial would be astronomical; given the extant evidence that injections are superior to topical antibiotics, surgeons might have ethical qualms about enrolling patients even if such a study were economically feasible.[13]

Dr. Shorstein is among a group of thought leaders seeking a path to FDA approval. "I had the good fortune to meet twice with Wiley Chambers, MD, who is a deputy director for ophthalmology products in FDA, along with David Chang, MD, the late Peter Barry and Nick Mamalis, MD, on behalf of ASCRS," he says. "Dr. Chambers felt that a prospective antibiotic study was feasible, and other avenues were probably less likely to be successful. I know that ASCRS has been thinking for quite a while now about how to achieve that holy grail of an FDA-approved drug. I don't think there's a clear solution yet, but we're working on it."

Dr. Tyson is less optimistic about FDA approval, but would like to see CMS change its posture on intracameral injections. CMS currently considers such injections as part and parcel of cataract surgery, not billable to the patient or recoverable to the surgeon. "We're trying to get this covered by Medicare. We're absorbing the costs ourselves as surgeons because it's entirely bundled within the surgery reimbursement. It would be great if we could get a pass-through designation for it, or if we could have patients sign an ABN stating that they could pay for it: We're saving patients hundreds of dollars and we're saving the Medicare system about 7 billion dollars projected over 10 years just by using this type of formulation versus drops," he says, referring to the CSIE study.

> *"In general, we respect the recent reports that have shown the devastating loss of vision in patients who are injected with vancomycin, and at Kaiser Permanente Northern California, we aren't routinely injecting it."*
> *— Neal H. Shorstein, MD*

The regulatory future of dropless and less-drops cataract surgery in the United States remains uncertain, but the protocol is becoming increasingly available with each passing year. Surgeons who want to implement it must look at the existing evidence, choose their therapeutic agents carefully and be willing to study their own outcomes to offer the most convenient and cost-effective treatments to patients without compromising safety and efficacy. "We're always looking for the best scenario for our patients," says Dr. Piracha. "It's evolved multiple times over the last four or five years, and it will probably continue to evolve." REVIEW

Dr. Tyson is a consultant for Imprimis Pharmaceuticals, Alcon, Allergan and Ocular Therapeutix. Dr. Piracha has received speaker's fees from Abbott Medical Optics. Dr. Shorstein reports no financial interests.

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Surgeons Make Do With The Tried and True

Walter Bethke, Editor in Chief

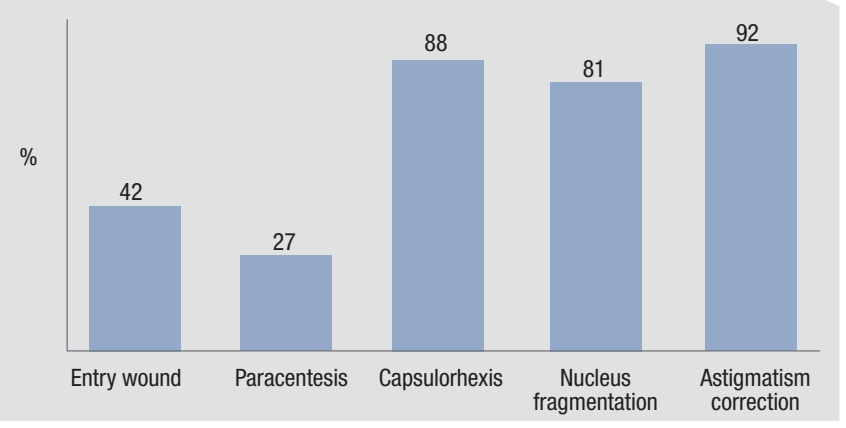
Surgeons mostly stick with what they know, but are intrigued by intraoperative aberrometry.

Recent years have seen a flurry of innovation in cataract surgery, but not a flurry of adoption of the new techniques and instrument technology on our e-survey. Surgeons appear to be content with their current methods for removing the cataract and managing the attendant steps, and appear to be taking a wait-and-see approach to the latest gadgets. The percentage doing femtosecond-assisted cataract surgery has stayed about the same on the survey, as has the percentage of surgeons experimenting with new ways to maintain a dilated pupil. A slightly larger percentage, however, are using intraoperative aberrometry, though many still make sure they do a good biometry preop, as well. These are just some of the results from this month's e-survey on cataract surgery techniques. This month, 927 of the 7,899 surgeons on our electronic mailing list opened the survey (11.7-percent open rate) and, of those, 81 completed the survey. Read on to see how your standards and practices jibe with theirs.

Intraoperative Tweaking

Surgeons may be warming up to the idea of checking their patients' intraocular lens powers during the cataract procedure via intraoperative

If They Use the Femto, What Do Cataract Surgeons Use It For?



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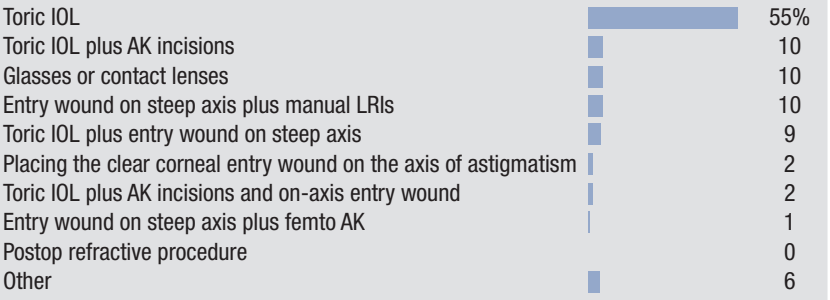


aberrometry.

On this year's survey, 28 percent of the respondents report using intraoperative aberrometry, vs. just 15 percent last year. A lot of them emphasize the technology's benefits for challenging cases. "Benefits: added comfort of accurate lens selection when it agrees with optical and manual biometry; it's extremely useful in post-refractive patients and high myopes; and it's excellent in guiding toric IOL axis," avers Howard Beach, N.Y., ophthalmologist Brian Collett. "Shortcomings: Needs clear media and it relies on accurate axial length and keratometry readings."

Anjali Tannan, MD, of Chicago, concurs with those who see its benefits in certain cases, "It's great for post-refractive patients," Dr. Tannan says. "Those are the only patients on whom I use it."

"Its benefits are that it increases your accuracy when using a premium IOL," says Matthew Fornfeld, MD, of Bloomington, Ind. "It also helps line up toric IOL's better than marking. The shortcomings are that it takes longer to do than a case in which it's not used, and it requires some judgment when it differs from preop calculations."

Though some surgeons are positive regarding intraoperative aberrometry, others are more circumspect. "The accuracy of sphere and axis alignment are good," says a surgeon from Indiana. "However, the [predicted] power in refractive surgery cases is not as good as anticipated." A surgeon from Texas doesn't see a lot of situations where it would be put to use at his practice. "It's time-consuming, involves cumbersome equipment and the measurements are taken under artificial conditions," he says. "As for benefits, it can help in decision-making when you're truly uncertain." Another Texan quips: "It's too cumbersome and time-consuming, with little obvious benefit."

Other Innovations

In addition to intraoperative aberrometry, surgeons weighed in on several new techniques and modalities being applied to cataract surgery.

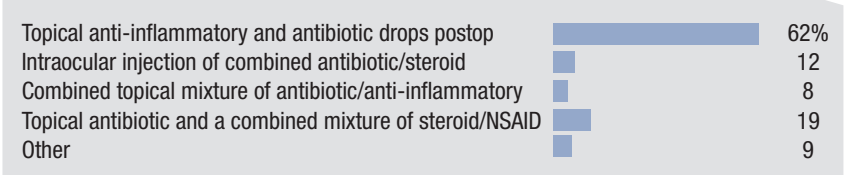
• ***Femtosecond-assisted cataract surgery.*** The percentage of surgeons on the survey who say they use the femtosecond laser for at least one step of cataract surgery stayed roughly the same as last year (32 percent vs. 36 percent in 2016). Their usage pattern on the survey has changed, however.

Last year, the entry wound and paracentesis were performed with the femtosecond by 57 percent and 43 percent of respondents, respectively. On the current survey, this has dropped to 42 percent and 27 percent. The percentages of surgeons who use it for the other steps of surgery appear in the graph on p. 46.

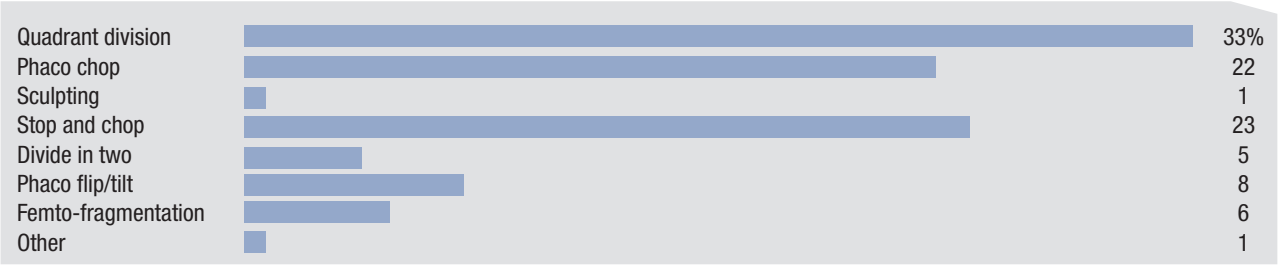
Clint Simpson, MD, of Lansing, Mich., thinks of femtosecond in this way: "My dislikes are the cost to patients, the fact that it slows surgical operation time by 20 to 30 percent, and involves a more challenging cortex removal," he says. "My likes are the consistent astigmatism correction nomograms and the perfectly centered rhexis. It's very helpful for traumatic lens cases, dense lens cases and weak zonule cases." New York's Dr. Collett sees some benefits, as well. "It's good for firm cataracts," he says. "It's also excellent for AK incisions and astigmatism reduction. It makes a perfect capsulorhexis. However, you can't use it with central corneal scars." A surgeon from Virginia also likes femtosecond technology. "It makes taking the cataract out much easier," he says. "It helps with the critical stage of the capsulorhexis and it's predictable."

Other surgeons on the survey, however, aren't as eager to go down the femtosecond road. "It's a solution looking for a problem," opines John Willer, MD, of The Dalles, Ore. A surgeon from Virginia has trouble seeing the benefit. "I'm not sure the results are any better according to surgeons who have used both,"

Steps Take to Avoid Infection (in Addition to Iodine)



Preferred Phacoemulsification Technique



he says. Stewart Gallaway, MD, of Crossville, Tenn., feels similarly, saying, "The accuracy of the corneal relaxing incisions is the only positive. The increased time and cost for little added benefit is the negative." A surgeon from Texas feels it gives "non-superior visual results and it's not any safer than manual phacoemulsification cataract extraction; it's also very costly technology."

• ***Managing miosis.*** For patients whose pupils won't cooperate, surgeons have some options. The most popular of these on the survey is an intracameral injection of epinephrine/lidocaine, chosen by 54 percent of the respondents. Eleven percent say they use Omidria (phenylephrine and ketorolac injection, Omeros) and 24 percent say they don't take any additional steps to promote a wide pupil during cataract surgery. Twelve percent choose some other approach to keeping the pupil manageable.

• ***Sedation.*** To accomplish preop sedation, the vast majority of the respondents (95 percent) still use intravenous sedation. Three percent say they use Imprimis' MKO Melt (compounded midazolam, ketamine HCl and ondansetron given sub-lingually). Three percent say they use another kind of method for sedation.

Dealing with Astigmatism

When the surgeons on the survey are faced with a patient with astigmatism, a toric IOL remains the most popular choice, chosen by 55 percent of respondents. Other popular options include combining a toric IOL with AK incisions (10 percent) and placing the entry wound on the steep axis as well as placing manual limbal relaxing incisions (10 percent). The rest of the astigmatism correction results appear in the graph on p. 47.

"Have good posture, stay relaxed and have fun."
— Jonathan B. Rubenstein, MD

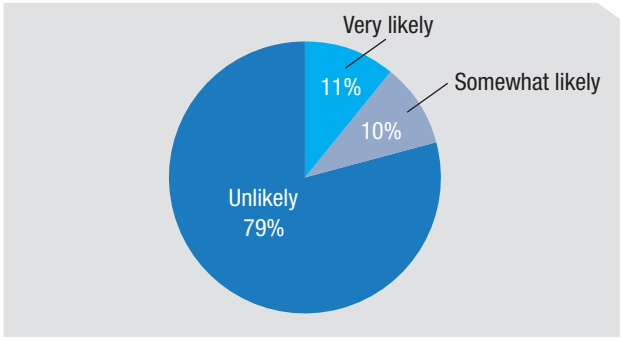
A surgeon from Texas says toric lenses provide "proven results, ease of technique, reasonable amount of additional time invested and no deleterious effects on quality of vision." David Flug, MD, of New York City says, "If your average preop vision is 20/60 or worse, a toric IOL does the job; if your average preop vision is 20/25 you need to get the astigmatism down to less than a half-diopter of cylinder (and you also need to rethink what you're doing in surgery)." A surgeon from Texas says that placing the entry wound on the steep axis and combining it with a femtosecond AK is his preferred option. "With that, the correction is accomplished easily," he avers. "For larger degrees of astigmatic correction, a toric lens is necessary. I place the incision on the axis of cylinder to reduce the toric power necessary for correction." Michigan's Dr. Simpson says it's not a one-size-fits all situation, but instead depends on how much astigmatism the surgeon is faced with. "I usually manage 0.5 to 0.75 D with the main incision placed on the steep axis," he says. "I manage 0.75 to 1.25 D with a temporal incision and paired femto astigmatic keratotomy. I manage anything from 1.5 to 4.5 D with toric IOLs. If the patient has over 4.5 D then I use a toric lens along with femto AK."

• ***Postop infection and inflammation prophylaxis.*** In this arena, the latest movement in some circles is toward dropless (injections) or less-drops (combined drugs in one bottle). Though a topical antibiotic and a topical anti-inflammatory drop are the single most popular method at 62 percent, the less-drops approach appears to be gaining some adherents on our survey. Nineteen percent of the surgeons use a topical antibiotic and a combined mixture of an NSAID and a steroid. Eight percent use a combination of antibiotic and anti-inflammatory in one bottle. Twelve percent of surgeons use an intraocular injection of a combined antibiotic and steroid.

Surgical Pearls

Surgeons also took time to share their tips and techniques for getting

Likelihood of Performing Femto Cataract Surgery in a Year



the best outcomes with cataract surgery.

Some of the surgeons gave advice on how to be in the proper mindset for surgery. Jonathan B Rubenstein, MD, vice-chairman and Deutsch Professor of Ophthalmology at Rush University Medical Center in Chicago, says, "Have good posture, stay relaxed, and have fun." A cataract surgeon from California advises his colleages to be "very picky about your ergonomics." Dr. Willer says to take every case seriously. "Never let your guard down or become complacent," he admonishes.

Other surgeons provided intraoperative advice. "Dont underestimate the power of verbal anesthesia," says Dr. Simpson. "Sometimes talking with the patient during the case can be more helpful than any additional IV sedation." Dr. Collett offers thoughts on incisions. "To make watertight incisions, use a 2.4 mm or smaller keratome, come into the corneal limbus flat in the plane of the iris and then aim slightly up in the corneal stroma but keep the heel of the keratome down," he says, emphasizing the last point. "You will then enter the chamber with a nice tight, flat and straight cut rather than a V-shaped cut." Ilan Hartstein, MD, of Los Angeles emphasizes the hydrodissection step. "Hydrodissection should involve rotating the nucleus before trying fracture techniques," he says, "and holding the cannula down so that fluid egresses from the wound." Dr. Flug says his best cataract tip doesn't involve phaco. "My secret weapon is the extracapsular extraction," he says. "It turns a phaco nightmare/disaster (such as a brunescent lens or loose zonules) into a routine case with great outcomes."

Finally, a surgeon from New Jersey says that, in the end, it's better to be good than fast. "Take your time with surgery; it's not a race," he says. "An extra minute to provide excellent outcomes is much more important." REVIEW


Redefining Primary Open-angle Glaucoma

Subdividing POAG patients based on factors other than low or high pressures might improve diagnosis and treatment.

Louis R. Pasquale, MD, FARVO, Boston

Glaucoma is the most common optic neuropathy in the world and a leading cause of blindness. We first became aware of it when Hermann von Helmholtz invented the ophthalmoscope in 1850. Unfortunately, 165 years later we still don't fully understand the nature of glaucoma—especially primary open-angle glaucoma. We do understand a few key things about it, most importantly that POAG is an intraocular-pressure-related optic neuropathy. The Baltimore eye survey reported that individuals with an IOP of 35 mmHg or more had a 39-fold increased risk of POAG compared to those whose IOPs were less than 17 mmHg. This clearly demonstrates a strong association between high IOP and the disease.

Meanwhile, ever-larger and better-constructed clinical trials, along with research, clinical observation and our growing knowledge of genetics, are expanding our understanding of the causes and mechanisms of glaucoma. However, as this evolution continues, the language we use when defining POAG and its subtypes is important. This is true because the assumptions built into our terms color our perceptions and expectations, as well as the research we choose to conduct and the treatment approaches we choose for our patients.

I believe our current terminology relating to POAG works against us by conflating and separating aspects of glaucoma in ways that are counterproductive and not supported by the evidence. For example, I believe we need to avoid equating POAG with high-tension disease—in other words, disease that occurs only in people who have pressures greater than 21 mmHg. Clearly, POAG can occur across a broad spectrum of intraocular pressures. Using terms such as low-pressure or normal-tension glaucoma is also misleading; it suggests that these individuals and high-tension glaucoma patients have different diseases, when in fact they may have overlapping pathologic features.

Here, I'd like to suggest a new way to subcategorize POAG that may be more useful than our current ideas about high- and normal-tension disease. I believe it would be helpful to divide glaucoma into at least three new subtypes: paracentral open-angle glaucoma, or PC-OAG; African-derived open-angle glaucoma, or AD-OAG; and estrogen-deficiency open-angle glaucoma, or ED-OAG. Dividing glaucoma into these subtypes—and potentially others—makes a good deal of sense because patients falling into these categories have: 1) distinct ages of onset; 2) different intraocular pressure profiles; 3) different optic nerve structural features; and 4) different genetic biomarkers tied to different biochemical pathways.

Paracentral OAG

Consider a 39-year old patient who came to see me for the first time 17 years ago. She was referred by the people at LensCrafters, who—to their credit—noticed a disc hemorrhage on her left optic nerve. When I examined her, I saw the disc hemorrhage and observed that the left optic nerve had some vertical elongation of the cup. Yet her slit lamp examination was normal; her IOPs were 18 mmHg and her corneal thicknesses weren't profoundly thin. To make matters even more interesting, I soon realized

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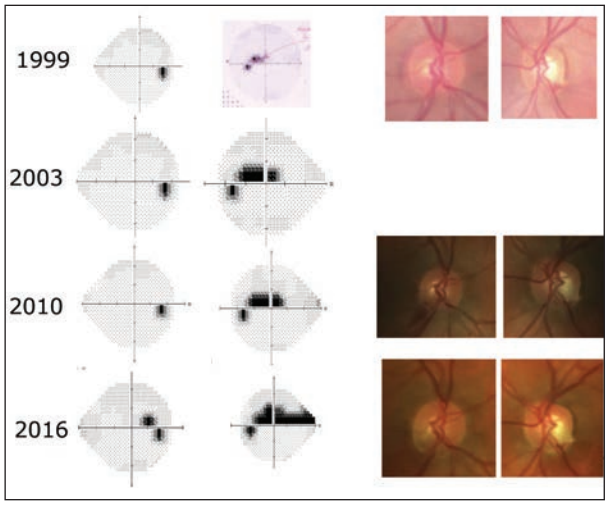
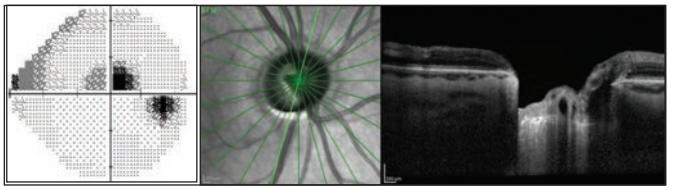


This patient continued to progress despite pressures in the low teens, with damage focused near the center of vision. Her father had higher pressures (24 mmHg untreated) and had lost most of his vision to glaucoma.



Many patients fitting the description of paracentral open-angle glaucoma have a triangular prelaminar neuronal defect within the cup that can clearly be seen on OCT.

that her father had been my patient for the previous nine years; he had advanced primary open-angle glaucoma. However, his untreated IOPs were much higher—24 mmHg.

This raises a question: How can it be that my 39-year-old patient, who might be diagnosed as having "normal-tension glaucoma," have a father who had "high-tension glaucoma?" The answer is most likely that the IOP we measure is not as important as the underlying genetic mechanisms of the disease. As you can see in the series of visual fields taken over the past 17 years *(above)*, despite my attempts to keep her pressures in the low teens, she continues to progress. In particular, notice how her disease is relentlessly attacking the center of her vision.

I propose that one subtype of primary open-angle glaucoma is an entity that can be referred to as *paracentral open-angle glaucoma*. We already know a fair amount about this type of glaucoma; it's certainly not new. Patients that I would place in this category have several distinct characteristics:

• ***A distinct structural profile.*** Many of these patients have a triangular prelaminar neuronal defect within the cup that can be seen on OCT. It's almost as if there's a little man with a shovel digging up this discrete neuronal segment of the prelaminar neuronal tissue *(above, right)*.

• ***Lower mean IOP.*** Compared to patients who have isolated nasal steps, patients with paracentral open-angle glaucoma tend to have a lower mean IOP. Consider the data from a 2011 study by Sung Chul Park, MD, and colleagues[1] *(below)*. Note that the mean IOP in the paracentral open-angle glaucoma cases was 21.6 ±4.5 mmHg. This is important because it means that some of the patients with this disease had IOPs that were close to 16 mmHg, while others had IOPs close to 24 mmHg. This example helps to illustrate why the concept of normal-tension glaucoma is bankrupt. PC-OAG happens across a spectrum of IOPs—albeit lower overall than the IOPs seen with isolated-nasal-step glaucoma patients.

• ***More disc hemorrhages.*** As shown in the same chart, the frequency of disc hemorrhages in paracentral open-angle glaucoma patients is much higher than it is in the isolated nasal step patients. In fact, I'd speculate that sooner or later, all patients with paracentral open-angle glaucoma will be discovered to have a disc hemorrhage.

• ***A different genetic signature.*** A study we published in 2013 found that patients with PC-OAG have some genetic markers that are significantly different from those of patients with isolated peripheral visual field loss.[2] Specific gene variants in the genomic regions between the caveolin 1 and caveolin 2 genes are more strongly associated with paracentral open-angle glaucoma than with patients who have primary open-angle glaucoma and isolated peripheral visual field loss.

We do have an idea why these variants may be important to the development of glaucoma. The caveolin variants are physically juxtaposed to endothelial nitric oxide synthase in biological membranes, indicating that these genes help to regulate the generation of nitric oxide. NO improves smooth muscle relaxation and is associated with lower IOP. It is interesting that new glaucoma drugs on

PC-OAG vs. Isolated Nasal Step OAG Patients

	Paracentral OAG (n = 69)	Isolated Nasal Step OAG (n = 53)	*p*-value
Maximum IOP (mmHg)	21.6 ±4.5	28.3 ±9.6	<0.001
Frequency of disc hemorrhage	44%	17%	0.001
Hypotension	16%	0%	0.001
Raynaud's phenomenon	23%	4%	0.002
Sleep apnea	9%	0%	0.03

Park et al. SC Ophthalmology 2011

the horizon, including rho kinase inhibitors, are known to influence NO signaling. The importance of NO for IOP regulation can also be seen in some animal-model studies, such as one reported in 2015 that showed that mice genetically engineered to be missing an enzyme that generates NO have elevated IOP and reduced aqueous outflow facility compared to wild-type mice who do have the enzyme.[3] (It's interesting to speculate that perhaps genetic markers in this region might represent the link between my patient referred by LensCrafters and her father. Of course, we don't know that for sure.)

Managing PC-OAG

When we're treating a patient with glaucomatous damage that's attacking the center of vision, two strategies may be especially effective.

• ***Suggest increasing the dietary intake of nitrate-rich vegetables.*** Given that NO is almost certainty a factor in this subtype of glaucoma, it occurred to me and several of my colleagues that something as simple as dietary consumption of foods high in nitrates—such as vegetables—might favorably modify the risk of POAG. (Patients often ask if there is something they can do to alter the risk of disease progression, and a dietary change is a good option to suggest.)

We looked at this because of something called the nitrate-nitrite-NO pathway, which is a source of exogenous NO that's well-known in the cardiovascular literature. When we consume vegetable nitrate, commensal bacteria in the mouth convert it to nitrite, which is very stable in our blood and can undergo either enzymatic or non-enzymatic conversion to NO. It's a simple and straightforward way to deliver NO.

To see whether this would really have an impact, we conducted a study, published in 2016, of the association between dietary nitrate intake and primary open-angle glaucoma in the Nurses' Health Study and the Health Professionals Follow-up Study.[4] Many of the participants in those clinical trials were followed for more than 25 years. As you can see in the chart above, participants who consumed a median of about 238 mg/day of nitrate from vegetables had a 44-percent reduced risk of primary open-angle glaucoma compared to those who consumed the smallest quantity of nitrates from vegetables, about 80 mg/day. This supports the idea that NO can help to prevent this subtype of primary open-angle glaucoma.

Consumption of Vegetables and Glaucoma Risk

433 PC-OAG cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p*-trend
Median nitrate intake	80 mg/d	114 mg/d	142 mg/d	175 mg/d	238 mg/d	
# cases	96	92	86	88	71	
MVRR*	1 (REF)	0.89	0.77	0.77	0.56	<0.001
95% CI		0.67-1.20	0.57-1.04	0.54-1.04	0.40-0.78	

*Multivariable Relative Risk

A 2016 study found that the greatest consumption of nitrate from vegatables (238 mg/d) was associated with a 44-percent reduced risk of PC-OAG compared to those who consumed the least (80 mg/d).[4]

To further confirm that NO signaling was associated with PC-OAG in particular, we separated those subjects with paracentral damage from those with peripheral visual field loss. Even though subjects with paracentral loss made up only about 25 percent of POAG cases, they were responsible for most of the association. (In subjects with peripheral visual field loss we found no statistical association with vegetable consumption.)

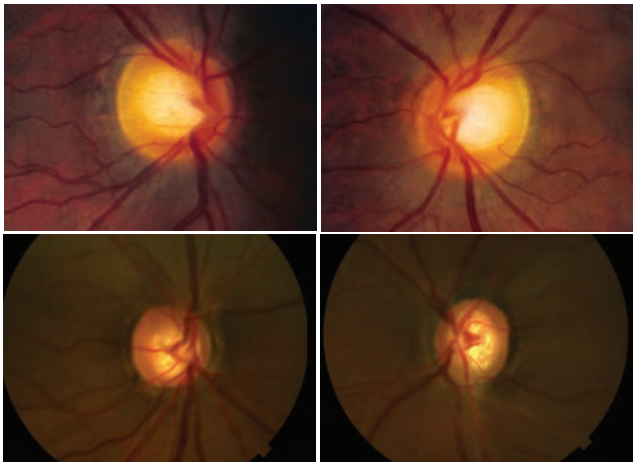
• ***Aim for a lower-than-usual target pressure.*** One other thing that I've noted in my two decades of managing patients with paracentral open-angle glaucoma: They require a lower target pressure than other glaucoma patients. For example, regardless of central corneal thickness, I've seen these patients progress at pressures lower than 16; that means 16 mmHg may be too high a pressure to help these patients. Ironically, another characteristic of this group of patients is that it can be very challenging to lower the IOP to the level required to stabilize their disease.

African-derived OAG

Another group of glaucoma patients with several unique characteristics is those of African descent. I refer to their group as having African-derived open-angle glaucoma, or AD-OAG. Among the characteristics associated with this category are:

• ***Early onset.*** For example, a 32-year-old African-American patient recently came to see me. He had a positive family history of glaucoma. Notably, he had lost most of his vision in the right eye some time ago; he had been told that he was essentially blind in that eye at an exam with another physician eight years earlier, at the age of 24. For whatever reason, his lost vision didn't seem to faze him, and he didn't pursue the matter.

When I examined him, he was unable to see the large E on the eye chart with his right eye, but was seeing 20/20 with the left. His untreated IOPs were 24 mmHg in the right eye and 18 in the left. His corneas were on the thin side, but a slit lamp examination didn't reveal any sort of secondary glaucoma. On gonioscopy, his angles were open. Scans revealed



AD-OAG is associated with early disease onset and reduced risk of disc hemorrhage. Top: 34-year-old patient. Tmax: 21 mmHg OU; CCT: 485 µm OU. Bottom: her 12-year-old daughter. Tmax: 12 mmHg; CCT 540 µm; visual fields normal.

that the right optic nerve was severely cupped and pale, and the visual field was essentially extinguished. His left eye showed some cupping, but a full visual field.

The fact that his vision was severely compromised by the time he was 24 means his glaucoma must have started when he was a teenager. His untreated IOPs were not extraordinarily high, although his central corneas were thin at 512 µm OD and 522 µm OS. There was no evidence of a secondary glaucoma. This might look like garden-variety primary open-angle glaucoma, but this combination of characteristics is pretty atypical, and that's why I would argue that it's a subset of primary open-angle glaucoma that deserves it's own category.

Another example: The images above show the discs of a 34-year-old woman of African descent and her 12-year-old daughter. The girl has normal pressures, corneas and visual fields; for this reason, the cupping seen in her discs might be construed as "physiologic." However, her mother has moderate-stage primary open-angle glaucoma with thin corneas and IOPs not much higher than her daughter's. You can see that she has erosion of both the inferior and superior neuro-retinal rims of both optic nerves. The odds are good that the cupping seen in her daughter's optic nerves is a sign of oncoming glaucoma.

Another indicator of this early onset phenomenon can be found in a study I co-authored with Richard Parrish II, MD, and Richard Lee, MD, in which they screened an Afro-Caribbean population living just south of Miami.[5] Their data revealed something very striking, but not surprising to me: Almost 21 percent of people between the ages of 20 and 40 had either an IOP ≥24 or a cup-to-disc ratio ≥0.7, in at least one eye. Normally, we worry about older patients developing glaucoma; this data demonstrates that younger people of African descent can indeed develop glaucoma.

• ***Reduced risk of disc hemorrhage.*** We know that, generally speaking, disc hemorrhages are a very important independent risk factor for POAG. That was demonstrated by three very well-done studies using multivariate models: the Ocular Hypertension Treatment Study; the Early Manifest Glaucoma Trial; and the Collaborative Normal Tension Glaucoma Treatment Study. After controlling for IOP, disc hemorrhage was either associated with conversion from ocular hypertension to primary open-angle glaucoma, or with disease progression (in people who had manifest open-angle glaucoma).

In contrast, the African Descent and Glaucoma Evaluation Study (ADAGES) examined close to 10,000 disc photos from people who were of African or Caucasian ancestry, both with and without glaucoma. The data showed that people of African descent had an 80-percent reduced risk of having a disc hemorrhage. In other words, even though African heritage is a risk factor for glaucoma and glaucoma blindness, and disc hemorrhages are known to be an important factor for disease progression, people of African ancestry seem to develop disc hemorrhages rather infrequently. At this point, we don't know the reason.

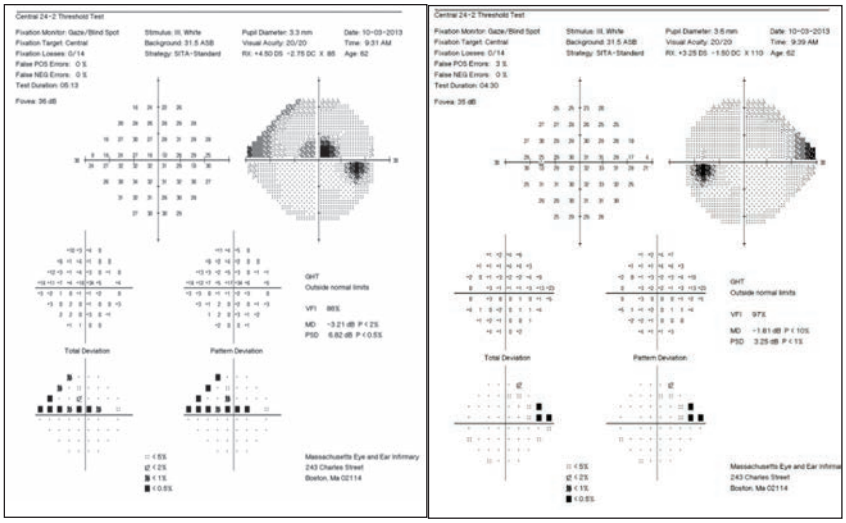
Managing AD-OAG

Given this, what can we do differently when managing a patient of African descent?

• ***Remember that this type of disease starts early.*** As you can surmise from the two case histories cited earlier, many of these individuals may be going blind because doctors tend to assume glaucoma isn't likely to be a problem until later in life. These younger individuals are simply not on our radar screen. So when faced with a young patient of African descent we should assume he or she might, in fact, have early glaucoma.

• ***Don't assume that the absence of disc hemorrhages indicates that the eye is healthy.*** These eyes, even when diseased, tend to have fewer disc hemorrhages than you might find in the eyes of individuals with a different subtype of glaucoma.

• ***Educate these patients about the nature of the disease, and offer to examine other young family members.*** When we see relatively young patients of African lineage who have significant disease, we need to ask about their children, because this disease starts early. This effort is being championed by my colleague Constance Okeke, MD, in Virginia. Patients can't be expected to know



Evidence suggests that estrogen levels may be associated with development and progression of glaucoma, as seen in this 61-year-old female patient.

that this is a risk, but if we're proactive and take the time to ask, we may be able to treat other family members before the disease has a chance to undermine their vision.

Estrogen-deficiency OAG

When seeing a female patient, we don't often focus on estrogen-related milestones in life, or related aspects of the patient's medical history. As a result, we may be missing a key glaucoma-related factor. Consider a 61-year-old Caucasian female patient I recently saw. She became a glaucoma suspect because of enlarged cups starting in the year 2000 when she was 47. She was status post hysterectomy; she'd had pre-eclampsia at age 30 and bilateral oophorectomy at age 53. In 2013 she noticed that the superior visual field in her right eye had collapsed.

When I examined her, she had concluded that her gynecological history had something to do with her vision loss. Her maximum IOP was 21 mmHg, central corneal thickness was 540 µm, and current IOPs on maximal medical therapy were 15 mmHg OD and 14 mmHg OS. Looking at her visual fields *(above)* the right eye has a superior paracentral scotoma; the left eye has a superior nasal step. Was this just another case of primary open-angle glaucoma? Or was she right in believing that her gynecological history had something to do with her eyes doing poorly?

It turns out there's a lot of evidence in the literature suggesting that the presence or relative absence of estrogen is associated with the development and progression of glaucoma. For example: Retinal ganglion cells have receptors for estrogen;[6] optic nerve structure varies with the menstrual cycle;[7] intraocular pressure decreases during pregnancy;[8] postmenopausal hormones lower IOP;[9,10] and retinal sensitivity on visual fields varies with the menstrual cycle.[11] Furthermore, increased risk of POAG is associated with later menarche;[12] oral contraceptive use;[12,13] early menopause;[14] and early oophorectomy.[15]

At the same time, events that extend estrogen exposure in a woman's life, such as later menopause or post-menopausal hormone use, are associated with reduced risk of open-angle glaucoma.[16-18] It's also been shown that estrogen eye drops protect against retinal ganglion cell dropout in a rat model of glaucoma.[19-21] In short, we have both clinical and population-based evidence that there may be a link between female reproductive health and POAG.

You may note that the damage seen in my patient's visual fields is reminiscent of the damage caused in patients with PC-OAG. The right eye has a superior paracentral scotoma, and the left eye has a superior nasal step. This makes sense, because estrogen is a strong upregulator of NO signaling, a fact that's well-demonstrated in the endocrine literature. So it's not surprising there would be some overlap between estrogen deficiency open-angle glaucoma and PC-OAG.

So: How can we better help these patients? The simple answer is to be aware that this aspect of our female patients' medical history may be very relevant to their potential for developing glaucoma or experiencing progression. Beyond that, it's premature to suggest any alteration of hormonal status based upon this connection; there are far too many ramifications associated with altering hormone levels, including possibly causing cancer. Even estrogen-based eye drops may have systemic effects, so being aware of the connection and this part of our patients' medical history may be the most we can afford to do—for now.

Practical Ramifications

Primary open-angle glaucoma is a remarkably heterogeneous disease. There are probably many candidate secondary mechanisms at work, including factors such as impaired NO signaling. I believe that thinking of glaucoma as consisting of subcategories like the ones I've described here—as well as other categories that may become evident in the future—will make it easier for us to help our patients by helping us catch early glaucoma that we might

otherwise have missed, and letting us offer treatments that are more precisely directed at the kind of glaucoma the patient is exhibiting. There is some overlap between PC-OAG, AD-OAG and ED-OAG, but they tend to have different ages of onset, different IOP profiles, different structural optic nerve features and different genomic biomarkers.

Making distinctions like this is also important for future research. If we lump all of these types of glaucoma together and just call them primary open-angle glaucoma, we're missing an incredible opportunity to learn about each of them. Effects associated with one subtype in a clinical trial could easily disappear into the overall numbers, leaving us with less understanding of the disease than when we started.

Here are a few clinical strategies that will help you make the most of what we already know:

• ***In PC-OAG cases, don't settle for a pressure of 16 mmHg.*** These patients need a lower pressure than that to prevent progression.

• ***Suggest eating more leafy green vegetables, especially if the patient has PC-OAG***. We have some pretty convincing cohort evidence that eating a diet high in leafy green vegetables could potentially help prevent the onset of open-angle glaucoma, especially if the patient has PC-OAG. The literature has also demonstrated that this is good for our cardiovascular health.

• ***When treating patients of African descent, make sure they understand that their young relatives need to be checked for the disease.*** You'll be surprised how often you'll find signs of the disease in young family members.

• ***Remember that "physiologic cupping" patients may be future glaucoma patients.*** When you encounter a patient who has a glaucoma-like disc but a full visual field—a patient you might assume has physiologic cupping—it's very reasonable to examine that individual once a year. We now know that there's a genetic predisposition to larger cups, and some of those genes are also associated with POAG.

• ***Take note of very high IOPs.*** The majority of POAG patients don't have IOPs greater than 35 mmHg. For example, consider the Barbados Eye Study. This study analyzed the IOPs of Afro-Caribbean patients newly converted to primary open-angle glaucoma. The data showed that the majority of glaucoma damage happened at pressures between 18 and 24 mmHg.[22] Like the African-derived patients we discussed earlier, these POAG patients typically don't have pressures of 40 mmHg.

At the practical level, this means that when you do see a pressure of 40 mmHg, the patient might have primary open-angle glaucoma, but you need to think about other secondary causes of elevated pressure such as steroid exposure or secondary glaucoma. Do a more careful slit lamp exam. Make sure the patient doesn't have exfoliation and isn't using steroids for some reason. (People using a steroid cream on their skin seldom realize that it might have an effect on their eyes.)

• ***Be wary of patients with rapid-onset glaucoma.*** No matter what type of glaucoma a patient may have, rapid visual field loss is rare. It does happen, but when you encounter a case like this you should always be looking for secondary causes such as steroid use or eye rubbing. Consider obtaining diurnal IOP curves, because their IOP could be much higher at other times of day. Also, some of these patients may have occult neuro-ophthalmological disease and require neuro-imaging. In short, your antenna should go up when you see a patient who progresses very rapidly in a short period of time. REVIEW

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The Foundation of a Good Formulation

Sometimes the other ingredients in an ophthalmic drug are almost as important as the active agent itself.

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When we make a choice about a therapeutic, most of our attention is focused on the active pharmaceutical ingredient. However, any given ophthalmic product is more excipient than drug substance. These 'inert' substances that act as diluent or vehicle to the active drug play an essential role in therapeutic effectiveness. The number of components in topical agents seems to be ever-increasing, yet we rarely stop to consider: "Why did they add that ingredient?" This month, we'll examine a variety of constituents found in ocular medications. Understanding the roles played by excipients is critical to tailoring therapy to the needs of your patients.

The Basics

If we were to postulate a primordial eye drop, we could imagine that it would contain a single active ingredient in plain water. But it doesn't take long to realize the limitations of such a formulation. Today, constituents of even the simplest preparations of aqueous drops must allow for sufficient ocular residence time and corneal penetration of the active drug; they must

be free from microorganisms, and have a suitable pH and tonicity to minimize irritation of the ocular surface and adverse effects. Often, the characteristics of excipients are multi-faceted, allowing them to perform more than one of these key functions.

Preservatives have been an essential component of multi-dose formulations, and can be classified according to their chemical characteristics, such as detergent (Polyquad), oxidizing (Purite) and chelating (edetate disodium) agents. Compounds such as EDTA have multiple functions, acting as a buffer for free divalents and preventing their buildup in the cornea, while also enhancing the antimicrobial action of other preservatives. Perhaps the most widely used preservative is benzalkonium chloride, a highly effective antimicrobial that's stable at a wide range of pH and temperature. While generally well-tolerated, there may be a concern in some patients that chronic use of one or multiple BAK-preserved topical medications may lead to ocular surface damage. Conversely, there have been many studies demonstrating the benefits and safety of this agent.[1] Overall, concerns about preservative effects have fueled the growing trend toward the use of preservative-free, single-dose formulations.

Control of pH through the addition of buffers is necessary not only for comfort, but also for drug stability and solubility. Since tear fluid has a very low buffering capacity, ophthalmic formulations contain excipients that maintain a pH range of 4.75 to 7.40. Topical products also require adjustment of tonicity close to that of natural tears. Generally, a range of 0.5% to 2% saline tonicity is well-tolerated. Irritating hypertonic solutions can induce tearing, which increases tear outflow and reduces the concentration and efficacy of the drug in the tears, while hypotonic solutions are often used effectively in tear substitutes to compen-

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sate for the high tonicity in the tears of dry-eye subjects.

Some excipients increase drug permeability and residence time in ocular tissues by enhancing corneal permeability, either by modifying the continuity of the epithelium, changing cell-to-cell junctions or altering the lipid/protein components of cell membranes. Often these effects are mediated by the same compounds that act as preservatives or buffers: chelating agents (EDTA); preservatives (BAK); surfactants (polyoxol 40); tonicity agents (NaCl, propylene glycol); and bile acid salts exhibit these properties, again lending credence to the multitasking nature of many excipients.[2,3]

Vehicular Variation

Topical instillation is the primary mode of administration for the treatment of anterior segment diseases.[4] Conventional products such as aqueous drops and solutions are relatively simple to formulate, have minimal storage limitations and are relatively easy to administer. Conversely, delivery and bioavailability are hampered by the rapid clearance and fluid turnover intended to maintain a stable tear film. The therapeutic dose delivered by a drop is quickly reduced by the action of blinking and nasolacrimal drainage. Only about 20 percent of the dose is retained in the pre-corneal pocket,[5] and less than 5 percent of that dose reaches deeper ocular tissues.[6] A key role of inactive constituents is to combat this physiological drive to clear added agents, and to prolong the effective residence time of the active drugs.

Ointments contain a non-irritating solid or semisolid hydrocarbon base with a melting point close to human body temperature, so that the combination of temperature and lid action yields an even distribution across the ocular surface. As we would expect, compared to ophthalmic solutions, ointments typically provide a longer contact time.[7] Ointments are usually applied at night before bed to minimize the blurred vision that occurs when the formulation spreads over the cornea, distorting optical quality. Use of an ointment lubricant right before bedtime is especially effective for individuals with dry eye, as the eye can recover during the night from the irritation and keratitis suffered all day because of an unstable and insufficient tear film. The ointment's micro-emulsion residence time is longer than daytime solutions, and the effects on vision aren't problematic during sleep.

Solubility enhancement is an important strategy when developing ophthalmic medications. Many drugs are poorly soluble in water, and substances must be added to increase solubility, raise the therapeutic concentration and improve bioavailability. Emulsions are oil and water mixtures that are homogenized to maintain uniformity. Emulsifying and suspending agents are added to a commercial ophthalmic emulsion such as Durezol (difluprednate) to enhance dispersion of the hydrophobic active ingredient from the oil phase into the aqueous mixture, creating a uniform product when shaken.[7] Additives that improve solubility include certain surfactants, caffeine, nicotinamide derivatives and cyclodextrins.[8-11]

Micro-emulsions improve drug permeation across the cornea and provide extended drug release that reduces the frequency of administration. These formulations are dispersions of oil and water that require surfactants and co-surfactants to enhance stability and penetration into deeper layers of ocular structures. Additionally, micro-emulsions possess low surface tension that aids in corneal spreading and mixing with the pre-corneal tear film. Despite the advantage of extended release and residence time, potential toxicity associated with high concentrations of surfactants may restrict their use.

For other hydrophobic drugs, an alternative to ointments or emulsions is the ophthalmic suspension, such as those used in Lotemax (loteprednol etabonate 0.5%) or Azopt (brinzolamide 1%). These include solid preparations that, when reconstituted, result in a suspension. The insoluble drug is made in a micronized form, and is dispersed in a suitable vehicle that contains excipients such as suspending agents, buffers and preservatives to improve solubility and prevent irritation of the cornea.[11] The limitation of suspensions, like emulsions, is that they must be shaken well before instillation.

Improved Formulations

Synthetic and natural polymers can be added to create a gel-like formulation; these improve the viscous and muco-adhesive properties of the drop, increase its residence time on the ocular surface, and slow its rapid dilution and drainage caused by tear-film turnover. Like ointments, these formulation enhancers melt at room temperature to release their constituents, but problems with blurred vision are less frequent. Many excipients possess multiple and overlapping properties, therefore combining various polymers holds promise for improved efficacy and greater compliance. Such additions can also lead to an advantageous reduction in dosing frequency.[12,13] Pilocarpine and some artificial tears are examples available in gel form.

Polymeric gels are classified into two groups: preformed and *in situ* forming, both of which are aimed to improve bioavailability. Preformed gels behave as simple viscous solutions that don't undergo modification after administration. *In situ* gelling systems contain polymers that undergo a solution-to-gel phase transition, forming a viscoelastic gel in response to external factors such as temperature, pH and the ionic strength in the tear film. These gels provide sustained drug release, prolong corneal contact time and re-

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quire less frequent applications.[14]

Primarily developed as injectables, hydrogels are also being investigated as topical drops to reduce dosing frequency of IOP-lowering medications.[15]

Colloidal systems are a liquid-retention drug delivery paradigm that employs a drug-loaded polymer carrier. Colloids consist of particles suspended in an aqueous solution that range in size from 10 to 400 nm. Corneal epithelial cells take up the particles by endocytosis. Colloidal forms include liposomes, nanoparticles and niosomes. These carriers are biodegradable and can be an alternative to implants that have to be removed surgically.

On the Horizon

In general, the next push of innovation involves chemical modifications of established carriers to revise or improve their formulation enhancing properties. For example, Novaliq (Heidelberg, Germany) is developing an innovative pharmaceutical formulation platform based on semifluorinated alkanes.[16] These SFAs can be used in various routes of administration to enhance drug efficacy. One such application, CyclASol, is a novel, non-aqueous and preservative-free formulation designed to enhance cyclosporine efficacy in dry eye. SFA in an aqueous formulation allows for delivery of the hydrophobic cyclosporine as a clear liquid, and is designed to improve tolerability and potentially reduce any blurring associated with emulsion-based formulations.

Another example of a new type of inactive ingredient comes from Kala Pharmaceuticals (Waltham, Mass.), which is developing a colloidal mucus-penetrating particle designed to enhance retention time by reducing mucus clearance of topically applied therapeutics. When applied to the surface of the eye, the particles spread out on the ocular surface and embed into the mucin layer, creating a depot of drug to diffuse into ocular tissues. Kala has conducted trials using a number of agents as treatments for conditions including postop cataract surgery inflammation, dry eye and meibomian gland disease, so this formulation technology should be in the pharmacy soon.

Drug development will always be a process of iterative refinement. It's important to keep in mind that progress doesn't always mean new therapeutics; just as often, improvements focus on solubility, enhanced retention or other means to maximize the net effect of an agent. There are many paths to success, and all have value. REVIEW

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Combo Therapy: When One Drug's Not Enough

A look at researchers' attempts to gang up on wet age-related macular degeneration.

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In our ongoing fight against exudative age-related macular degeneration, we're often forced to cast about for new treatments in situations where current methods come up short. Fortunately, there are several methods or drugs that can be used to treat AMD, principally anti-vascular endothelial growth factor injections[1] and, to a lesser extent, photodynamic therapy.[2] Each treatment has its advantages and disadvantages. The pathogenesis of AMD is complex, however, so not all treatments can achieve the desired effect in every patient. In an effort to boost our success rate, and since inflammation is one of the important factors underlying the development of CNV, physicians and researchers have tried combination treatments using an anti-inflammatory drug in cases of refractory wet AMD. In some instances, they've achieved promising results.[3,4] In this article, we take a look at combination therapy and its possible benefits.

Pathogenesis of Exudative AMD

To see the potential of combination therapy, it helps to understand the pathogenesis of CNV due to AMD. Unfortunately, the mechanism behind the CNV isn't completely understood.

The retina receives long-term exposure to light radiation and is therefore vulnerable to oxidative damage. With aging, light-damage accumulation and free-radical injury, the retinal pigment epithelium can be damaged by oxidative products.[5] Oxidative stress, in turn, can promote the expression of VEGF mRNA and transcription, supporting theories regarding the important role of oxidative damage in the formation of CNV.[6]

Apart from the oxidative damage mechanism, many studies have shown that AMD is a chronic, non-specific inflammatory disease.[7] Using immunohistochemistry, research has confirmed that AMD eyes have retinal tissue autoantibodies, suggesting that from early to late AMD, retinal antibodies play an important role in the disease's pathogenesis.[8] Additionally, elevated levels of C-reactive protein, a marker of systemic inflammation, have been shown to be a risk factor for AMD.[9]

Based on our current knowledge of the complex mechanisms of AMD, one can understand that if only anti-VEGF treatment is given, in some cases AMD may not be fully controlled, and clinical observation has confirmed that there is indeed a subset of patients not responsive to anti-VEGF monotherapy.[4]

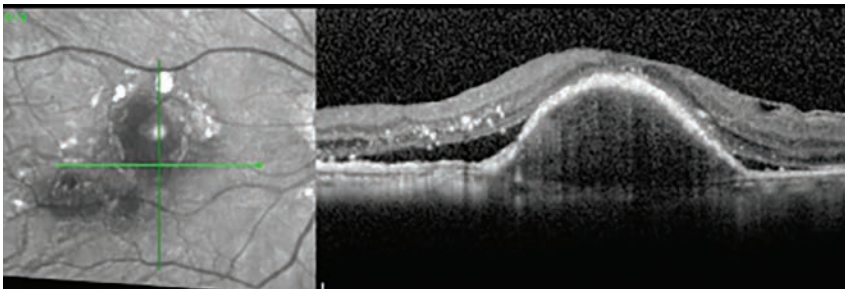

Figure 1. Incomplete response to anti-VEGF monotherapy. Shown here is a 72-year-old woman with neovascular AMD with persistent subretinal fluid and pigment epithelial detachment following serial ranibizumab and aflibercept injections.

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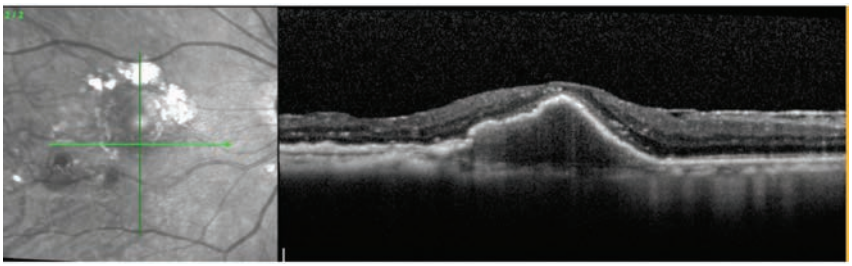

Figure 2. The patient from Fig. 1, showing improvement in exudation after combined anti-VEGF and steroid treatment. There is resolution of subretinal fluid after one dexamethasone intravitreal implant injection in this patient, who had persistent fluid despite monthly anti-VEGF injections.

The Limits of Monotherapy

PDT with verteporfin was approved in the United States for the treatment of wet AMD in 2000.[10] The Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study showed that the visual acuity benefit of verteporfin therapy for AMD patients with predominantly classic CNV subfoveal lesions is safely sustained for two years, supporting the use of verteporfin therapy for these cases. For AMD patients with subfoveal lesions that are minimally classic, however, there is insufficient evidence to warrant routine use of verteporfin.[11] PDT was a milestone in the development of treatments for wet AMD, but patients still generally lost vision despite receiving the treatment, and multiple treatments were often required. The typical patient required five to six treatment sessions during the first two years of follow-up.[12]

Anti-VEGF therapy was an important breakthrough in the treatment of wet AMD and has replaced PDT as the most effective treatment. For example, mean visual acuity changes from baseline were +6.6 and 10.7 letters after 12 months of follow-up in the pivotal MARINA[13] and ANCHOR[14] trials, respectively. However, 5 to 10 percent of patients with wet AMD didn't completely respond to anti-VEGF in these studies, even with monthly injections for two years.[13,15] This suggests that there is room for improvement in clinical outcomes in at least some patients with wet AMD *(See Figure 1)*. Meanwhile, the possibility of reducing the overall number of treatments is attractive, as long-term injection increases the treatment burden for the patient and could also increase the risk of complications.[16] Combination therapy has been suggested by some as a means of addressing these shortcomings.

Combination Approaches

Following is a list of combination therapies currently available to us, and how well they perform.

• ***PDT and steroid injection.*** Combination therapy has been used to treat patients with wet AMD for a number of years. The first combination therapy consisted of PDT combined with intravitreal triamcinolone acetonide. A study of this approach demonstrated a reduction in the need for retreatment compared with patients receiving PDT alone.[17] Another study showed that combination therapy with PDT and intravitreal TA improved visual acuity and reduced treatment frequency.[18] However, this combination therapy was limited by complications such as cataract and glaucoma,[19] as well as the relative lack of visual improvement that characterized PDT treatment when compared with anti-VEGF.

• ***PDT and anti-VEGF.*** Since anti-VEGF is the most effective monotherapy, some investigators have tried

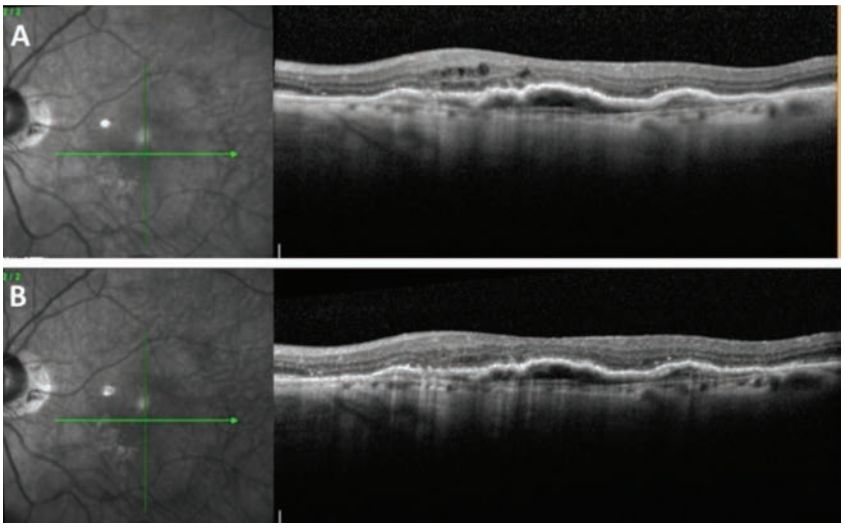

Figure 3. Control of residual exudation with supplemental dexamethasone intravitreal injection in an 85-year-old woman receiving aflibercept injections at baseline. (A) Intraretinal fluid is present despite monthly aflibercept injections. (B) Improvement one month following a dexamethasone intravitreal implant injection.

a combination approach in order to enhance the duration of action or efficacy. One group investigated the safety and efficacy of combination therapy with intravitreal ranibizumab with PDT for patients with wet AMD and found that it was more effective than PDT alone, but this study didn't assess whether combination therapy was superior to ranibizumab monotherapy.[20] Two other uncontrolled, prospective studies showed benefit with a combination of anti-VEGF and PDT.[21,22]

• ***Anti-VEGF and steroids.*** Both VEGF secretion and inflammation are principal factors contributing to CNV in AMD so, theoretically, combining anti-VEGF with steroid therapy could yield a better outcome than monotherapy. In one study, researchers implanted the dexamethasone intravitreal implant (Ozurdex 0.7 mg; Allergan, Irvine, Calif.) in patients who were already receiving monthly ranibizumab injections who had persistent fluid. The researchers found that the combination treatment promoted complete or partial resolution of fluid in all eyes.[4] Another study found that the adjunctive use of the dexamethasone intravitreal implant reduced the need for ranibizumab reinjection during six months of follow-up when compared with sham injection.[23] In our practice, too, we've combined anti-VEGF with a dexamethasone intravitreal implant for the treatment of refractory wet AMD. In a small cohort of patients, we've observed improvement in the clinical course, with resolution of fluid after introduction of steroid to the treatment regimen *(See Figures 2 and 3).*

In the future, new agents addressing other pathogenic aspects of wet AMD may offer additional benefit in combination with current therapies. In the meantime, combining anti-VEGF and steroid medications may offer a worthwhile treatment option in patients with persistent fluid despite regular anti-VEGF treatment. REVIEW

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Dr. Stewart is a consultant for Forsight Vision4. Dr. Kong has no financial interest in any of the products discussed.

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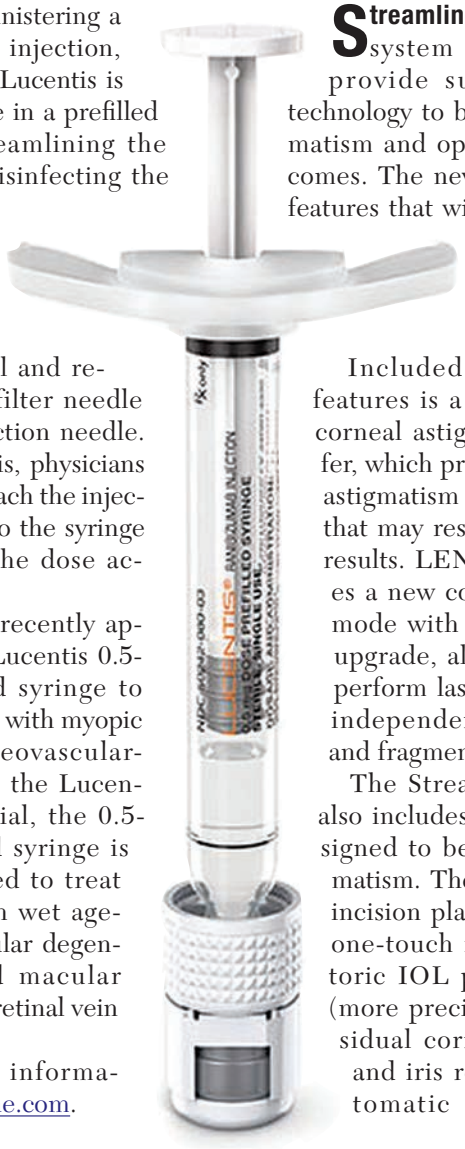
FDA Approves Prefilled Lucentis Injection

For physicians looking to eliminate several steps in preparing and administering a ranibizumab injection, Genentech's Lucentis is now available in a prefilled syringe, streamlining the process of disinfecting the vial, attaching a filter needle, drawing medicine from the vial and replacing the filter needle with an injection needle. With Lucentis, physicians need only attach the injection needle to the syringe and adjust the dose accordingly.



The FDA recently approved the Lucentis 0.5-mg prefilled syringe to treat patients with myopic choroidal neovascularization. Like the Lucentis 0.5-mg vial, the 0.5-mg prefilled syringe is also approved to treat patients with wet age-related macular degeneration and macular edema after retinal vein occlusion.

For more information, visit gene.com.

LENSAR's Streamline III Upgrade

Streamline III, LENSAR's new system upgrade, seeks to provide surgeons with the technology to better manage astigmatism and optimize patient outcomes. The new upgrade contains features that will optimize surgeon confidence, safety, efficiency and laser precision, says LENSAR.

Included in the upgrade's features is a new wireless total corneal astigmatism data transfer, which provides more precise astigmatism treatment planning that may result in better postop results. LENSAR also introduces a new corneal incision-only mode with the Streamline III upgrade, allowing surgeons to perform laser corneal incisions independent of capsulotomy and fragmentation.

The Streamline III upgrade also includes other features designed to better manage astigmatism. These include: arcuate incision planning (allowing for one-touch incision planning); toric IOL power conversions (more precise reduction of residual corneal astigmatism); and iris registration and automatic cyclorotation adjustment (compensates for cyclorotation, eliminating the need for corneal ink marking).

For more information on the Streamline III upgrade, visit lensar.com/features.

OD-OS's Navilas Laser System 577s

For surgeons looking to streamline laser-therapy planning, OD-OS's Navilas 577s allows for physicians to digitally pre-plan the entire laser therapy based on fundus and diagnostic images.

The Navilas laser system 577s is a retinal photocoagulator that comes integrated with a digital fundus camera. According to OD-OS, the Navilas is used for the treatment of diabetic macular edema, proliferative diabetic retinopathy, subretinal neovascularization, retinal vein occlusion, lattice degeneration, retinal tears and retinal detachments. The Navilas is also used for both color and infrared imaging of the retina.

OD-OS adds that the Navilas offers focal treatments without a contact lens and infrared illumination, which enhances patient comfort. The company also says the device's large field of view and assisted pattern positioning improve panretinal and focal treatments.

For more information on OD-OS's Navilas 577s, visit od-os.com.

This article has no commercial sponsorship.

Tips for Fixating IOLs With Gore-Tex Sutures

A step-by-step guide for suturing the Akreos and the Cz70BD intraocular lenses.

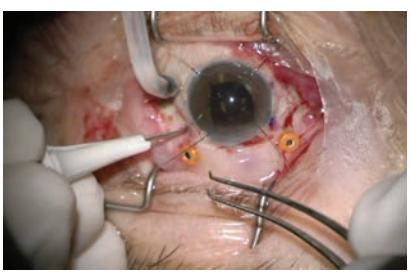
Kevin Rosenberg, MD, Syracuse, N.Y.

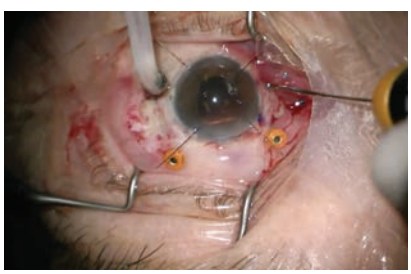
Advancements in phacoemulsification techniques have revolutionized the field of cataract surgery, making it a relatively straightforward procedure. However, cases still arise where the capsular bag is violated and there's insufficient support to place an IOL in the bag or sulcus space. In these situations, there are several options available to the surgeon to make sure the IOL gets placed securely. These include using an anterior chamber intraocular lens, an iris-fixated posterior chamber IOL or a scleral-fixated PCIOL. Though various techniques for scleral-fixated IOLs have been described over the years, in this column I'll describe a "real-world," modified technique using Gore-Tex sutures for the Bausch + Lomb Akreos AO or the Alcon Cz-70BD.

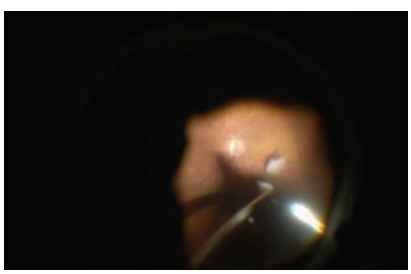
Technique

As a retina surgeon, I typically get patients referred to me for scleral-fixated PCIOL implantation when either the capsular bag has been violated intraoperatively and the patient is left aphakic with retained lens material or when a patient's existing IOL/bag complex has subluxated out of the visual axis or has dislocated into the vitreous cavity. Following is a description of the technique I use in such cases.

• ***Scleral wounds.*** I make a conjunctival peritomy down to bare sclera at the 3- and 9-o'clock positions. I then use external cautery (eraser tip) to cauterize any bleeding vessels in the scleral bed, and insert three 23-gauge, valved trocars 3.5 mm from the limbus in the standard fashion in preparation for pars plana vitrectomy. The first trocar goes in the inferotemporal quadrant, the next one in

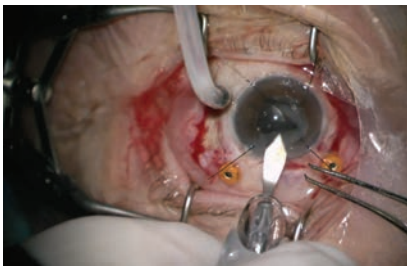
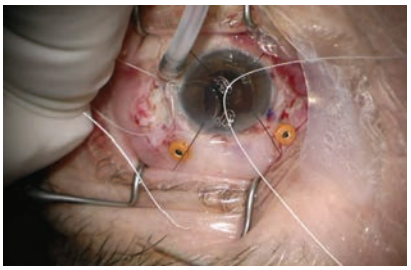
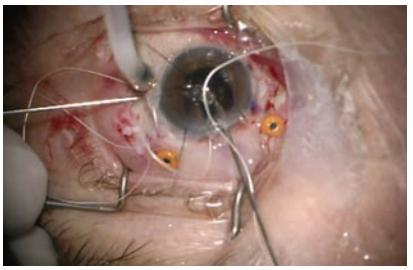






(From left to right) Figure 1: After the three trocars are inserted in a standard three-port pars plana vitrectomy setup, with the infusion in place, the 23-gauge MVR blade is used to create four additional sclerotomies, two on the nasal side and two on the temporal side. These sclerotomies should be 4 mm apart on each side and equidistant from the corneal marks at the 3- and 9-o'clock positions. Figure 2: An Alcon 23-ga. Maxgrip forceps is used to enter the sclerotomy sites. I then complete a vitrecomy and lensectomy (if lens particles have fallen back into the vitreous cavity). Figure 3: If an IOL has dislocated into the vitreous cavity, I retrieve it from the posterior segment. Fig. 3 shows the vitrectomy and lensectomy.

This article has no commercial sponsorship.

(From left to right) Figure 4: The surgeon uses a 2.75-mm keratome blade to create a triplanar incision at 12 o'clock. Figure 5: The Akreos lens is laid onto the corneal surface and CV8 Gore-Tex sutures are threaded through the lens eyelets. Figure 6: The distal suture end on the temporal side is introduced through the corneal wound and is transferred intraocularly to the bent Maxgrip forceps and externalized though the distal sclerotomy.

the superotemporal quadrant and the last one in the superonasal quadrant, all done in a beveled fashion. I then insert the infusion into the inferotemporal trocar and set it at a pressure of 25 mmHg. When performing this step of the procedure, make sure to insert the trocars slightly more superior and inferior than usual (away from the horizontal meridians) to make room for the additional sclerotomies to come.

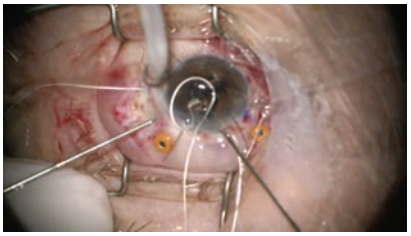
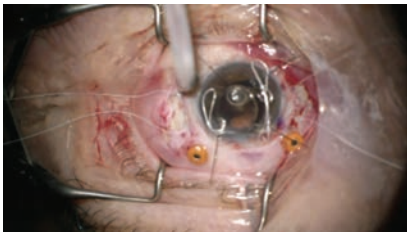
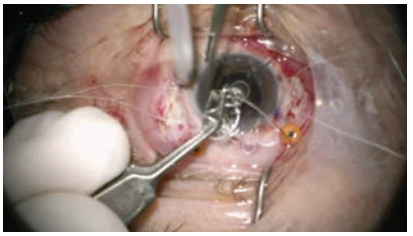
I use a toric marker to place two marks on the cornea 180 degrees apart, one at 3 o'clock and the other at 9 o'clock. I use calipers to make two marks 4 mm apart on either side of the sclera, 2.5 mm from the limbus. This amounts to two marks nasally and two marks temporally. The scleral marks should straddle and be equidistant from the corneal marks previously created to ensure proper lens centration. I then use the 23-ga. MVR blade (without the trocar) to create four sclerotomies, one at each of the marks that I just created *(See Figure 1, opposite page)*. I use a 23 ga. Maxgrip forceps (Alcon) to enter each of these fresh sclerotomy sites to ensure their patency *(See Figure 2, opposite page)*. It's at this phase of the procedure that I complete a vitrectomy and a lensectomy if lens particles have fallen back into the vitreous cavity, and will also retrieve a dislocated IOL, if need be *(See Figure 3, opposite page)*. It's also important to note that, depending on how much manipulation has been done to the eye or is planned, I have a low threshold for 360-degree prophylactic laser at the ora serrata to prevent postoperative retinal tears and detachment.

• ***Corneal incision.*** I then create a triplanar corneal incision at the 12-o'clock position and enlarge the wound on either side to a diameter of approximately 4 mm *(See Figure 4)*.

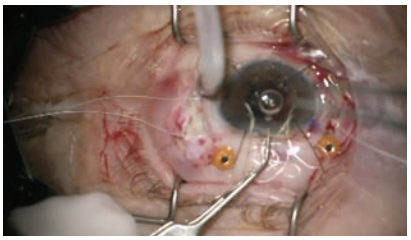
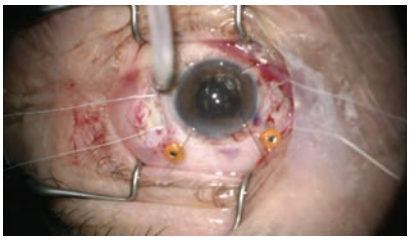
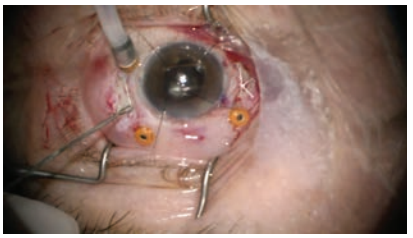
A common pitfall to watch out for at this point in the procedure is shelving of the wound, so make sure to create a clean corneal incision. If shelving occurs, the suture and IOL may become caught in this incision during its introduction.

• ***Suturing.*** I then lay the lens onto the corneal surface in the correct orientation, with the two eyelets with notches oriented in the upper right and lower left corners. I cut a CV8 Gore-Tex suture—with the needles removed—in half. One half is threaded through the two nasal eyelets and the other half is threaded through the two temporal eyelets *(See Figure 5, above)*. Using two Maxgrip forceps (one in each hand), I use the "handshake" technique to externalize the sutures through the sclerotomy sites on both sides.

You can use a hemostat to bend one of the Maxgrip forceps to facilitate the suture hand-off. One Maxgrip forceps is used to grasp the end of the distal Gore-Tex suture on the temporal side and the suture end is introduced through the corneal incision. In the other hand, the bent Maxgrip forceps enters the distal sclerotomy site on the temporal side. The suture end is now passed off to the bent Maxgrip forceps and is then externalized through the distal sclerotomy site *(See*

(From left to right) Figure 7: The proximal suture end on the temporal side is introduced through the corneal wound and is transferred to the bent Maxgrip forceps and externalized through the proximal sclerotomy. Figure 8: The Gore-Tex sutures have been externalized through the four sclerotomy sites on both the temporal and nasal sides. Figure 9: The lens is "taco folded."

(From left to right) Figure 10: After being taco-folded, the lens is manually inserted into the anterior chamber. Figures 11 and 12: The lens lies flat in the eye and the Gore Tex sutures are tied down in a 3-1-1-1 fashion on both sides.

Figure 6).

I use the same technique to externalize the proximal end of the suture on the temporal side, and then externalize this end through the proximal sclerotomy *(See Figure 7)*. Next, I use this handshake technique to externalize the distal and proximal Gore-Tex sutures on the nasal side *(See Figure 8)*.

I insert Viscoat through the corneal wound to coat the endothelium and fill the anterior chamber, and clamp the infusion. At this point, I fold the lens in a "taco" shape with a tie forceps, and introduce it into the anterior chamber *(See Figures 9 and 10)*. I gently pull the sutures on either side and the lens slides behind the iris plane.

A potential complication at this step is the sutures tangling intraocularly, which will result in the IOL not lying flat when it's inserted. To avoid this entanglement, you have to pay meticulous attention to suture placement. If you notice the intraocular lens isn't lying flat after insertion, check to see if one of the sutures is tangled on one of the contralateral eyelets, which is rather common. Attempt to untangle the suture with a Maxgrip forceps. If this isn't possible, then remove either the temporal or the nasal suture, depending on the one that's tangled. Then, reintroduce the suture, thread it through the two eyelets intraocularly, and then externalize the two suture ends.

Once the lens is properly inserted intraocularly, I tie the Gore-Tex suture in a 3-1-1-1 fashion on both sides and bury the suture knot using one of the forceps *(See Figures 11 and 12, above)*. Before locking the suture on either side, make sure the lens is well-centered. Also make sure the lens isn't pulled so tightly that the eyelets bow on either side, which can lead to astigmatism.

• ***Closing the case.*** At this point, I close the corneal incision with 10-0 nylon sutures, take one more look at the retina and then remove the three trocars. If there's any leakage, I close the sclerotomy with a 6-0 plain suture *(See Figure 13, below)*.

At this stage, it's crucial to ensure that the four additional sclerotomy sites aren't leaking. You should have a low threshold for closing any or all of them with 6-0 plain sutures to avoid postoperative hypotony and choroidal detachment.

Finally, I close the conjunctiva at the limbus at the 3- and 9-o'clock positions and make sure that the Gore-Tex sutures are covered by the conjunctiva *(See Figure 14, below)*. If the conjunctiva isn't covering the Gore-Tex sutures completely, or the patient's conjunctiva is extremely thin, there's a significant risk of exposure of the suture, which can lead to endophthalmitis. If necessary, you can suture Tutoplast (IOP Ophthalmics) over the sutures to prevent exposure.

The scleral-sutured Akreos or Cz70BD IOL using a Gore-Tex suture is an effective technique to use when there's a lack of capsular support for an in-the-bag or sulcus placement. It's important to note that the Akreos lens is hydrophilic acrylic, however, so there's a theoretical risk of lens opacification when intraocular gas is used. Knowing this, in my own personal experience, if a postoperative retinal detachment occurs, SF6 gas is preferable to C3F8 in order to prevent potential complications from prolonged gas exposure. REVIEW

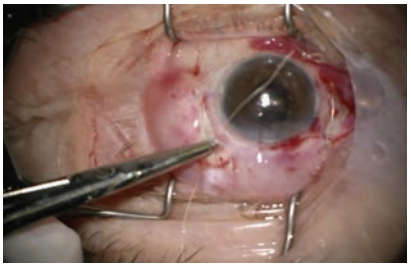
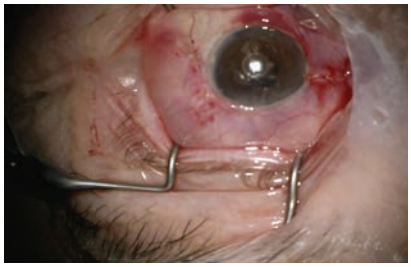



Figure 13 (left): Close the sclerotomy sites with 6-0 plain suture, if leaking. Figure 14 (right): The conjunctiva is closed over the Gore-Tex sutures at 3 and 9 o'clock.

Dr. Rosenberg is in private practice at Retina Vitreous Surgeons of Central New York and is a clinical associate professor at SUNY Upstate Medical University.

Suggested Reading:
1. Cao, D, et al. Akreos Adapt AO Intraocular lens opacification after vitrectomy in a diabetic patient: A case report and review of the literature. BMC Ophthalmol 2016; doi: 10 10.1186/s12886-016-0268-3.
2. Khan, A, Gupta O, Smith R, et al. Scleral fixation of intraocular lenses using Gore-Tex suture: clinical outcomes and safety profile Br J Ophthalmol doi:10.1136/bjophthalmol-2015-306839.



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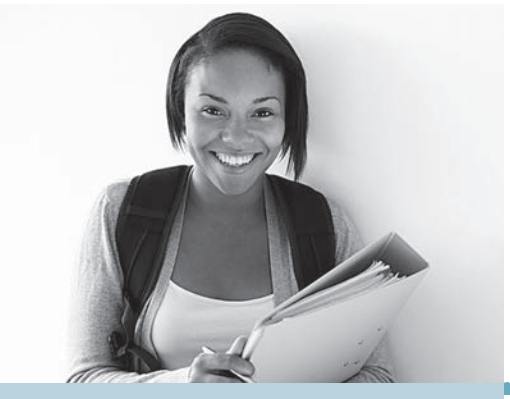

About Rick

Rick Bay served as the publisher of The *Review* Group for more than 20 years.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

Scholarships are awarded to advance the education of students in both ***Optometry*** and ***Ophthalmology***, and are chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

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Chemotherapy-Induced Epiphora

Using relevant articles listed in PubMed, researchers looked at the evaluation and management of chemotherapy-induced epiphora, punctal and canalicular stenosis and nasolacrimal duct obstruction. Researchers selected abstracts based on the following keywords: epiphora; tearing; punctal stenosis; canalicular stenosis; nasolacrimal duct obstruction; chemotherapy; 5-FU; docetaxel; S-1; mitomycin C; capecitabine; imatinib; and radioactive iodine. If the corresponding article was deemed relevant and appropriate, it was included for review.

The relevant studies demonstrated that the chemotherapeutic drugs best documented to cause epiphora are 5-flourouracil and docetaxel, and that the main mechanism underlying epiphora is canalicular stenosis. The drugs that are less-commonly reported to cause epiphora include S-1, capecitabine imatinib, topical mitomycin C and radioactive iodine treatment of papillary thyroid carcinoma. Despite the above-mentioned drugs' association with epiphora, some drugs and administration schedules cause only punctal and canalicular inflammation, whereas others cause significant canalicular stenosis. Weekly administration of docetaxel is far more likely to cause canalicular stenosis than administrating it every three weeks, researchers found. S-1 and radioactive iodine have been reported to cause nasolacrimal duct obstruction. Early recognition of punctal and canalicular stenosis or nasolacrimal duct blockages, and early intervention with topical steroids and canalicular stenting in patients at risk for permanent canalicular scarring, are important to avoid the need for more invasive and complicated procedures, say the researchers.

The investigators say that the broad study of research from PubMed clearly demonstrates that a variety of chemotherapeutic agents have been reported to cause epiphora, and some of these drugs have also been found to cause obstructions of the lacrimal drainage system. They add that early recognition and management of epiphora is important because it leads to better outcomes.

Ophthal Plast Reconstr Surg 2017;33:9-12
Mansur C, Pfeiffer M, Esmaeli B.

Outcomes of LOVIT II

In a follow-up to its first trial, the Veterans Affairs Low Vision Intervention Trial II sought to determine the value of low-vision rehabilitation with a therapist. compared with LV services without intervention. LOVIT II complemented LOVIT by comparing the outcomes of two types of LV programs for veterans less severely visually impaired from the effects of macular diseases.

This randomized clinical trial looked at 323 veterans with macular diseases and best corrected distance visual acuity of 20/50 to 20/200. Anonymous interviewers administered questionnaires by telephone before and after LV treatment. Using an intention-to-treat design, participants were randomized to receive LV devices with no therapy or LV devices with a rehabilitation therapist providing instruction and homework on the use of LV devices, eccentric viewing and environmental modification. Visual ability was measured in dimensionless log-odd units (a 0.14-logit change in visual ability corresponds to the change expected from a one-line change in visual acuity).

Of the 323 participants, the mean age was 80 years, and 314 were male. Basic LV was effective in improving visual ability. However, the LV rehabilitation group improved more in all visual function domains except mobility. Differences were 0.34 logit in reading (p=0.05), 0.27 logit in visual information (p=0.04), 0.37 logit for visual motor tasks (p=0.01) and 0.27 logit overall (p=0.01). In stratified analyses, the LV rehabilitation group with best-corrected distance visual acuity in the better eye between 20/63 and 20/200 improved more in visual ability (reading, visual motor and overall). Differences were 0.56

logit in reading ability (p=0.02), 0.40 logit for visual motor tasks (p=0.04) and 0.34 logit overall (p=0.02). There was no significant difference between treatment groups for those with better eye BCDVA of 20/50 to 20/63.

Based on these results, both basic LV alone and LV combined with rehabilitation were effective, but the added LV rehabilitation only increased the effect for patients whose BCDVA in the better eye was between 20/63 and 20/200. Researchers say basic LV services may be sufficient for most LV patients with mild visual impairment.

JAMA Ophthalmol 2017;135(2):96-104
Stelmack J, Tang C, Wei Y, et al.

Cross-Linking for Keratoconus

In a retrospective, single-center, non-randomized study, researchers sought to report the long-term outcomes of corneal collagen cross-linking for progressive keratoconus in pediatric patients. Spectacle-corrected distance visual acuity, retinoscopy, topography and tomography pre- and postop at three and six months, one year and annually thereafter.

A total of 377 eyes of 336 pediatric patients (aged 8 to 18 years) with progressive keratoconus underwent epithelium-off CXL. Of these, 194 eyes had a follow-up beyond two years and up to 6.7 years. At last follow-up, there was significant improvement in mean CDVA from 0.33 ±0.22 to 0.27 ±0.19 logMAR (p≤0.0001); a reduction in mean topographic astigmatism from 7.22 ±3.55 to 6.13 ±3.28 D (p=0.0001); a mean flattening of 1.20 ±3.55 D in maximum keratometry (p=0.0002); and a mean corneal thinning of 31.1 ±36 µm (p<0.0001). The mean change in Kmax was most significant in moderately advanced keratoconus (average keratometry 48 to 53 D). Central cones showed more corneal flattening than peripheral cones. Stabilization or flattening of Kmax was seen in 85 percent of eyes at two years and in 76 percent after four years. Stabilization or improvement of CDVA was seen in 80.1 percent of eyes at two years and 69.1 percent after four years.

In a majority of pediatric eyes, CXL remains an effective way to stabilize keratoconus for longer than two years. Flattening of Kmax was greater in moderately advanced keratoconus and in central cones. Long-term follow-up beyond four years, however, revealed that a few eyes showed features suggestive of the reversal of CXL.

Cornea 2017;36:138-143
Padmanabhan P, Reddi S, Rajagopal R, et al.

Equipment and Supplies / Career Opportunities

OPHTHALMOLOGY

Bassett Healthcare Network
Bassett Medical Center

Bassett Healthcare Network, a progressive health care network in central New York and major teaching affiliate of Columbia University is seeking a **General Ophthalmologist** to join a busy ophthalmology department based in the lovely village of Cooperstown. Glaucoma experience a plus!

Bassett Healthcare Network is an integrated health care system that provides care and services to people living in an eight county region covering 5,600 square miles in upstate New York. The organization includes six corporately affiliated hospitals, as well as skilled nursing facilities, community and school-based health centers, and health partners in related fields.

KEY BENEFITS OF THIS POSITION:

- Opportunities exist for both research and teaching if interested.
- Currently there are specialists in retina, cornea, pediatrics and oculoplastics.
- The support staff is well trained and experienced in both the clinic and operating room.
- Group employed model with competitive salary
- Comprehensive benefit package, including but not limited to medical, dental, CME, relocation assistance and paid malpractice insurance

Bassett Medical Center is located in Cooperstown, New York, a beautiful resort village on Otsego Lake. Home to the National Baseball Hall of Fame and Museum, the Glimmerglass Opera Company, and the Fenimore Art Museum, the area also boasts many cultural and four season recreational advantages including theater, music, museums, golf, sailing, hiking, and skiing.

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or visit our web-site at www.bassettopportunities.org

Practice For Sale

A middle-aged man presents with a presumed case of choroidal hemangioma.

Aditya Kanesa-Thasan, MD and Carol Shields, MD

Presentation

A 52-year-old man was referred to the Wills Eye Hospital's Ocular Oncology Service for further evaluation of progressive vision loss in his left eye. He had been diagnosed with a choroidal hemangioma following evaluation elsewhere by both a retinal specialist and ocular oncologist, and had received four injections of the anti-vascular endothelial growth factor drug bevacizumab for overlying subfoveal fluid, with minimal improvement. He was therefore referred for recommendations of how to proceed with treatment.

Medical History

The patient's ocular history was otherwise notable for myopia with astigmatism (-8 D OU). His past medical history included hypertension, hyperlipidemia and migraines, and his medications were verapamil and rosuvastatin calcium. He was allergic only to moxifloxacin. Family history revealed glaucoma and diabetes mellitus. He was a nonsmoker and drank alcohol socially.

Examination

On ophthalmic examination his best corrected visual acuity was 20/20 in the right eye and 20/70 in the left eye. His pupils were equal, round and reactive to light without relative afferent pupillary defect. Extraocular movements and confrontation visual fields were full bilaterally. Intraocular pressures were 14 mmHg by applantion in both eyes. External and anterior segment examinations were unremarkable. A dilated funduscopic examination of the right eye was within normal limits. The left eye showed an elevated macula, suggestive of an underlying tumor, along with related retinal pigment epithelial changes. Despite the elevation, the choroidal vascular tissue appeared of normal color and its architecture was without a visible tumor, suggesting that the mass might be deeper than the choroid *(See Figure 1)*.

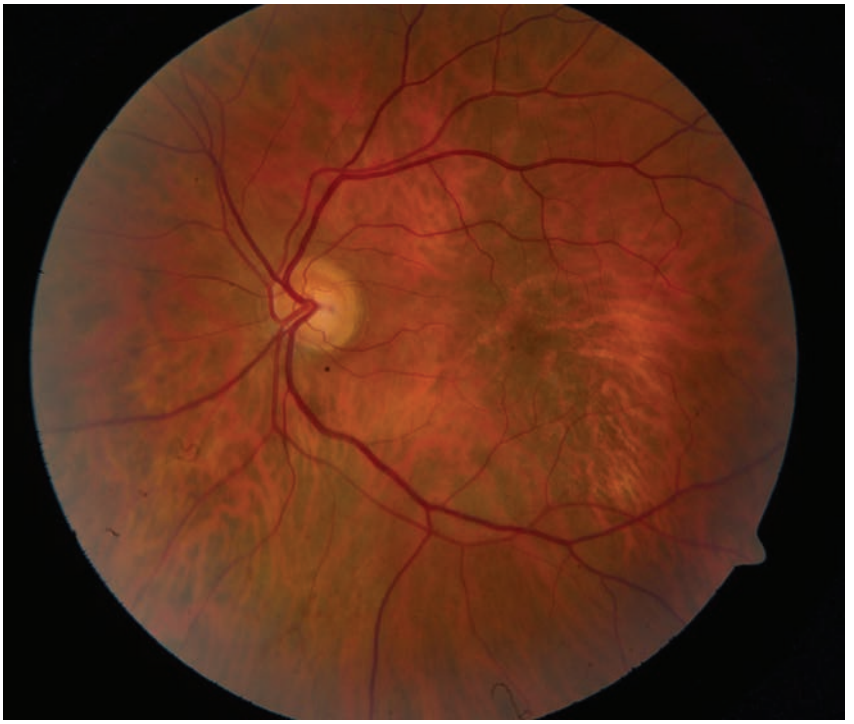

Figure 1. Fundus photograph of the left eye showing an area of central macular RPE alterations and no visible tumor.

What is your differential diagnosis? What further workup would you pursue? Please turn to page 76.

Diagnosis and Workup

Given the inconclusive examination findings, further evaluation was pursued with multiple modalities. B-scan ultrasonography of the left eye demonstrated a convex echodense thickening underlying the macula, measuring 3.38 mm at its thickest point *(See Figure 2)*. Fluorescein angiography was consistent with a large area of RPE atrophy in the macular region which extended inferiorly in a trough-like pattern *(See Figure 3)*. There was also a pinpoint area of leakage superiorly on late images *(See Figure 4)*. Indocyanine green angiography showed normal filling of the choroidal vasculature *(See Figure 3)* with "window defects" of increased transmission at the area of RPE loss and later mild generalized hypofluorescence with focal slight hyperfluorescence at the site of leakage *(See Figure 4)*. EDI-OCT of the left eye showed an area of abrupt scleral thickening underneath the macular region with a shallow subfoveal retinal detachment, choroidal thinning and loss of outer retinal details *(See Figure 5)*. These imaging features, coupled with the patient's history, were inconsistent with the referral diagnosis of circumscribed choroidal hemangioma and were more suggestive of a diagnosis of dome-shaped macula.

The patient was diagnosed with DSM in the left eye. He was noted to have features of DSM in the right eye as well, but was visually asymptomatic. An MRI of the orbits was performed to rule out a mass causing external scleral compression, and confirmed no evidence of solid tumor in either orbit. The patient was continued on monthly anti-VEGF injections in the left eye, but BCVA did not improve and the subretinal fluid persisted. It was determined that since the patient did not respond to anti-VEGF treatment, observation would be indicated.

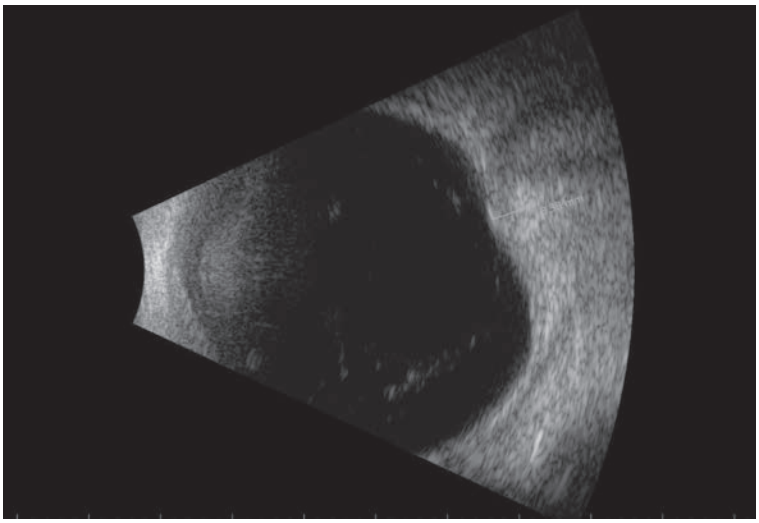

Figure 2. B-scan ultrasonography of the left eye showing a convex, echodense elevation of the posterior pole, measuring 3.38 mm in thickness.

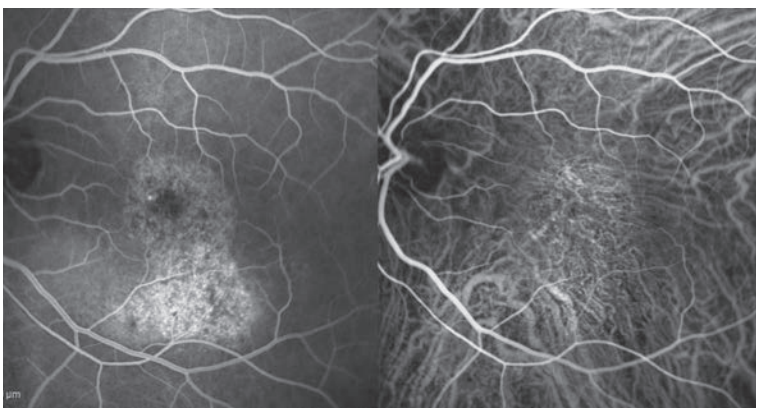

Figure 3. Venous phase FA (left) and ICGA (right) images of the left eye 19 seconds after dye injection. FA shows a trough-like area of RPE atrophy (a "window defect") with stippled hyperfluorescence and a pinpoint area of hyperfluorescence in the nasal foveal region. ICGA shows a similar window defect and normal filling of the choroid.

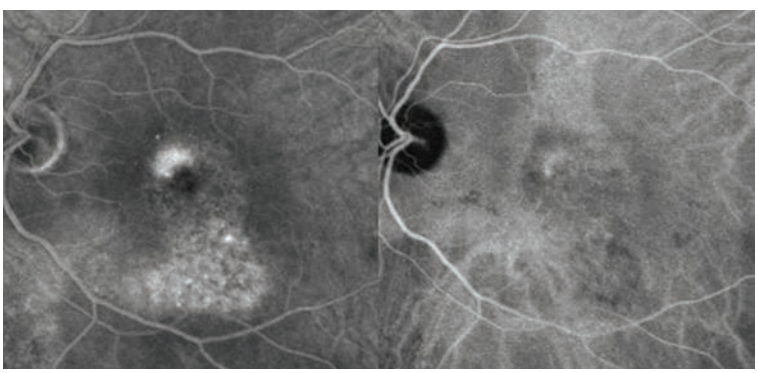

Figure 4. Late FA (left) and ICGA (right) images of the left eye approximately nine minutes after dye injection. FA shows leakage superiorly and ICGA shows a generalized hypofluorescence in the macular area with a small area of hyperfluorescence in the foveal region.

Discussion

Dome-shaped macula was first described in 2008 in a retrospective review of OCT images in highly myopic patients who noted the onset of unexplained visual loss.[1] In the study, this abnormality was characterized as a dome-shaped elevation of the macula within a posterior staphyloma and was found to be associated with shallow subfoveal detachment on OCT in 10 of 15 eyes. Additionally, the authors noted areas of RPE atrophy and pigment clumping on FA with corresponding areas of hypofluorescence on ICGA. Focal points of leakage were also present on FA in seven of 15 eyes as seen in the presented case. Much like our patient, the median refractive error was -8.25 D. The location of the observed focal thickening on B-scan ultrasonography in patients with DSM was initially unclear,[1] as it could not be determined whether it was localized to the choroid, sclera or both. However, the widespread use of EDI-OCT has permitted detailed visualization of the choroid and sclera, making close examination of the extent of their involvement in DSM possible. Other researchers described a retrospective case series of 23 eyes with DSM imaged with EDI-OCT and found that the macular elevation was due to scleral prominence, not choroidal thickening.[2]

Clinical features of DSM can overlap with those of a circumscribed choroidal hemangioma.[3] This benign tumor classically occurs in the macular region and, like DSM, can demonstrate echodensity on B-scan ultrasonography with overlying subretinal fluid. Uniquely, FA and ICGA show hyperfluorescence with hemangioma and hypofluorescence with DSM. In addition, EDI-OCT adds the important differentiating feature of choroidal expansion with hemangioma rather than scleral expansion as seen with DSM. One report described a series of 10 consecutive cases of circumscribed choroidal hemangioma imaged with EDI-OCT.[4] In contrast to scleral changes seen in DSM, EDI-OCT revealed prominent thickening of the choroid between the RPE and sclera and demonstrated the smooth, gently sloping curve of the choroidal hemangioma. There was no evidence of staphyloma in these patients. The average height of the hemangiomas by EDI-OCT measurement was 1,187 µm, and the choroidal vessels in the region of the tumor were found to be expanded without compression of the choriocapillaris. This helps to further differentiate from DSM, as these patients will have scleral convexity with overlying normal or compressed choroidal tissue.

The pathogenesis of DSM has not been elucidated. There are several theories regarding the etiology of the scleral thickening in this condition. One hypothesis is that scleral thickening may be a mechanism to compensate for anisometropia in myopic patients.[5] Others have implicated ocular hypotony, tangential vitreomacular traction, resistance to deformation, or asymmetric staphyloma development as possible causes.[6] Long-term follow-up of patients with DSM has revealed a tendency toward progression of scleral thickening over time.[7] In one series, the mean height of the DSM increased from 338.9 to 364.3 µm over a mean 38-month follow-up period (p=0.007).

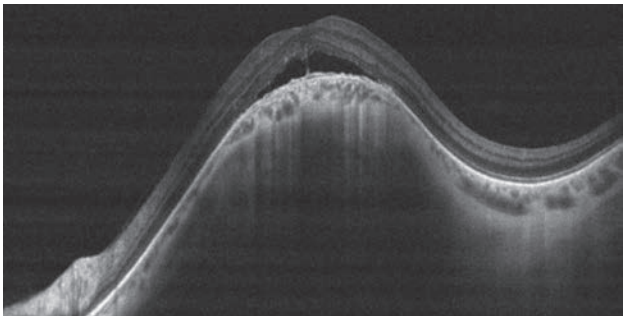

Figure 5. Horizontal raster EDI-OCT slice through the fovea of the left eye. Note the abruptly increased scleral thickness with slight thinning of choroid on the slope, and slight thickening of choroid at the apex. There was associated subretinal fluid at the height of the scleral bulge. No choroidal mass was present.

The extent of choroidal abnormality in DSM is also unclear. Two large studies of patients with DSM have shown that the central choroidal thickness in patients with DSM doesn't differ significantly from myopic eyes without DSM.[8,9] Nonetheless, there's a significantly higher ratio between central and peripheral choroidal thickness in eyes with DSM.[9] An alternative series showed increased central choroidal thickness in patients with DSM.[10] Increased choroidal thickness has also been positively correlated with the height of the scleral bulge and the presence of serous retinal detachment.[11]

To date, there's no treatment consensus for DSM-associated visual disturbance. In general, treatment is aimed at reducing the associated subretinal fluid. Anti-VEGF has shown some promise in myopic patients with DSM and concurrent choroidal neovascularization,[12] but other patients have been refractory to such treatments.[13,14] Photodynamic therapy,[13,15] laser photocoagulation[13] and spironolactone[14,16] are among alternative therapies that have been tried. These have all had variable efficacy in reducing subretinal fluid and metamorphopsia and have had mixed results in terms of improving long term visual acuity. Reports have also suggested that the subretinal fluid may resolve spontaneously in some individuals.[7,17] Further studies are needed to establish the superiority of any one therapy as well as to elucidate the prognostic factors for successful visual recovery.

REVIEW

Resident Case Series

In recounting this case of a patient initially diagnosed with a circumscribed choroidal hemangioma who eventually proved to have DSM, we seek to highlight this recently described entity. Despite its established characteristic clinical presentation and findings on diagnostic testing, the pathogenesis and effective treatment modalities for DSM remain undetermined. We look forward to future research endeavors that will enable us to better understand DSM and its management. REVIEW

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